Therapies for Spastic Esophageal Motor Disorders

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Objectives

1. Describe potential pharmacologic treatment options for spastic esophageal motility disorders
2. Describe outcomes related to endoscopic dilation and botulinum toxin injection for treatment of spastic esophageal motility disorders
3. Describe patient selection for utilization of esophageal myotomy for the treatment of esophageal motility disorders

Introduction

Spastic esophageal disorders have been variably defined over the years, but with the advent of high-resolution esophageal manometry (HRM) and esophageal pressure topography as well as the Chicago Classification, the term "spastic disorders" now refers to type III achalasia, distal esophageal spasm (DES), and hypercontractile esophagus (HE). Type III achalasia is notable for functional outflow obstruction and aperistalsis with premature contractions. DES also has premature contractions but no outflow obstruction. HE is characterized by increased esophageal body contractility. The Chicago Classification version 4.0 criteria for each of these disorders, as well as representative Clouse plots, are shown in Fig. 33.1. Overall, the spastic disorders represent a rare diagnosis seen on HRM. Recent studies have estimated achalasia prevalence at 18/100,000 in patients under 65 years and 162/100,000 in those over 65 years, and of the three subtypes, type II achalasia is thought to be the most prevalent. HE represents approximately 2–3% of manometric diagnoses, and DES likely another 3–4%. Progression from HE or DES to achalasia is uncommon but can occur. The exact pathophysiology of these disorders remains unclear but represents a neural imbalance in the form of decreased inhibition, excess contractile drive, or both. These affect the smooth muscle anatomy and/or function and lead to spasm. Clinically relevant disorders typically manifest with dysphagia, chest pain, regurgitation, and/or reflux. Because of their unclear pathogenesis and heterogeneity, treatment decisions should be guided and measured.

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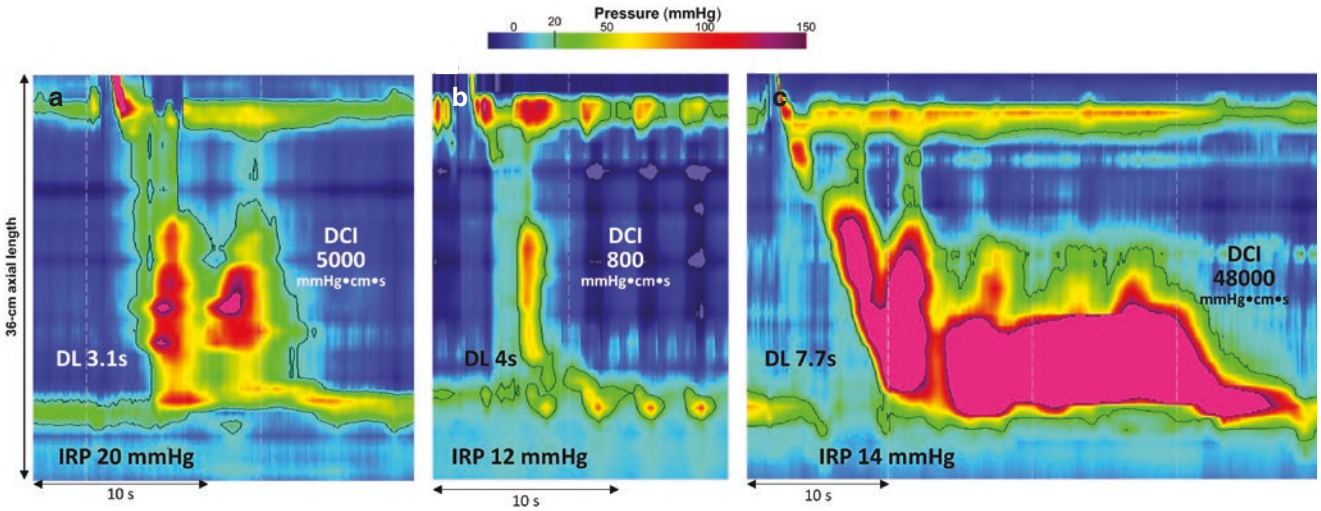

Fig. 33.1 Chicago Classification v.4.0 criteria and manometric representations of the spastic esophageal disorders. High-resolution manometry test swallows from three patients are displayed (**a**–**c**). (**a**) Type III (spastic) achalasia with esophagogastric junction (EGJ) outflow obstruction reflected by an elevated integrated relaxation pressure (IRP) in addition to the premature swallow reflected by the lower-than-normal distal latency (DL). (**b**) Distal esophageal spasm is represented by the premature swallow and normal EGJ outflow pressure. (**c**) Hypercontractile esophagus is represented by the hypercontractile swallow with greater-than-normal distal contractile integral (DCI), in addition to normal EGJ outflow pressure and normal DL

Approach to Management

The management of spastic esophageal disorders is multifaceted and depends upon etiology and pathogenesis, clinical symptoms, and objective data. For HE and DES, clinical symptoms must be present in order for the diagnosis to be considered clinically relevant. The primary reported symptoms are dysphagia, seen in 53–67% of HE and 32% of DES patients, and chest pain, seen in 29–47% of HE and 22% of DES patients. Atypical symptoms are also reported but should be approached with caution when making treatment decisions. Additionally, secondary causes of spasm should be assessed and ruled out. Considerations include gastroesophageal reflux disease (GERD), opiate use, and mechanical obstruction. Finally, in suitable patients with confirmed type III achalasia, management should be more aggressive than in HE or DES, as pharmacologic therapy alone is known to be the least effective achalasia treatment option.

Pharmacologic Therapy

Medications in treatment of spastic motor disorders are primarily used for HE and DES and are aimed at symptom reduction and reduction of contractile abnormalities. Treatment can be challenging due to the heterogeneity of etiologies but is typically initiated toward the primary presenting symptom. Perceptive symptoms, such as chest pain, may respond slightly better to proton pump inhibitors and/or neuromodulators, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or trazodone. Mechanical symptoms, such as dysphagia, may respond better to therapies directed at relaxing the smooth muscle; however, notable overlap can occur. Overall, there are limited data for the treatment efficacy of any of the medications, as large, randomized, placebo-controlled studies are rare. In addition, some studies have suggested that esophageal motor abnormalities can change over time, thus creating variability in symptom persistence among patients. The various pharmacologic options are detailed below. Dosing and side effect profiles are noted in Table 33.1. Of note, many of the agents used for smooth muscle relaxation can worsen GERD if present.

Calcium Channel Blockers

Blocking L-type calcium channels leads to reduction of intracellular calcium, thus inhibiting smooth muscle contraction. This effect can decrease esophageal contractile amplitude and relax the lower esophageal sphincter (LES). A randomized, placebo-controlled study in achalasia showed that nifedipine and verapamil both decreased LES pressure, and nifedipine also decreased esophageal body contraction amplitude. Unfortunately, neither significantly improved symptoms. Nifedipine has thus been used with limited success in achalasia but may still be considered for treatment of

Table 33.1 Medications used to treat spastic esophageal disorders

Medication class	Proposed dose	Common adverse effects
Calcium channel blockers	Nifedipine 10–30 mg before meals, diltiazem 180–240 mg/day before meals	Headache, constipation; hypotension
Nitrates	Isosorbide dinitrate 5–10 mg before meals	Headache, flushing, dizziness, hypotension
PDE-5 inhibitors	Sildenafil 50 mg (can be multiple times per day)	Headache, dizziness, hypotension, pedal edema
Peppermint oil	10 mL peppermint oil in water; OTC peppermint tablets also used (2 tabs before meals)	Heartburn, allergic reactions
PPIs	Variable; treat as GERD	Headache, diarrhea, nausea, vomiting
TCAs	Amitriptyline 10–50 mg at bedtime (also used: nortriptyline, imipramine, desipramine, all at similar doses)	Drowsiness, constipation, dry mouth, tremor, jitteriness, QT prolongation
SSRIs	Sertraline 50–200 mg daily, paroxetine 5–50 mg daily, citalopram 20 mg daily	Nausea, dry mouth, bowel changes, headache, abnormal ejaculation, decreased libido, insomnia
SNRIs	Venlafaxine 75–150 mg daily	Sleep disturbances, nausea, anorexia, dry mouth, abnormal ejaculation
Trazodone (SARI)	100–150 mg daily	Dizziness, drowsiness, fatigue

Note off label use for listed medications as treatments of esophageal chest pain or dysphagia

HE and DES. Diltiazem is thought to have similar effects and is often considered for chest pain symptoms. Small trials of nifedipine and diltiazem in DES have been mixed with regard to effects on chest pain and dysphagia.

Nitrates and Phosphodiesterase (PDE-5) Inhibitors

Increased nitric oxide allows for LES relaxation and decreased contractility. Small trials have shown both manometric and symptom benefit of nitrates in non-reflux-related DES. However, large, controlled trials in either DES or HE are lacking. PDE-5 inhibitors block the degradation of nitric oxide, thus enhancing its inhibitory effects on the smooth muscle. Despite this, symptom improvement is not consistently reported among patients with motor disorders. Sildenafil was the first in this class to show improvement in LES pressure, esophageal contraction amplitudes, and symptoms in patients with spastic disorders. Similar results were seen for vardenafil and tadalafil, but cost and lack of insurance coverage can present a barrier for patients.

Peppermint Oil

Peppermint oil is a relatively safe and inexpensive option that can be used to reduce spastic contractions. Originally evaluated by Pimentel et al. peppermint oil was found to eliminate simultaneous contractions seen on esophageal manometry. Khalaf et al. expanded on this to show improvement in symptoms of non-obstructive dysphagia and chest pain in patients with esophageal motility disorders.

Proton Pump Inhibitors

Acid inhibition with proton pump inhibitors is thought to address the issue of concomitant GERD frequently seen in patients with spastic disorders. In cases of GERD confirmed by pH testing, PPIs can be considered a first-line therapy. Their use has also been shown to ameliorate perceptive symptoms of non-cardiac chest pain (NCCP), as GERD is by far the most common cause of NCCP. Some mechanical symptoms noted in this patient population may also be improved with PPIs. That said, the actual efficacy in DES and HE as currently defined has yet to be fully elucidated.

Neuromodulators

The role of neuromodulators in visceral hypersensitivity is well described, and both visceral hypersensitivity and psychiatric comorbidities have been suggested as mechanisms in patients with NCCP. In this population, TCAs have proven successful in up to 75% of patients who have incomplete response to acid-suppressive therapy. In one randomized, open-label trial of patients with NCCP, adding amitriptyline to rabeprazole improved global symptom score significantly more than doubling of the rabeprazole dose. Imipramine has also been shown to be effective at relieving NCCP in patients with esophageal motility disorders. Another well-designed trial of patients with hypersensitive esophagus showed improved symptoms with citalopram, a commonly used SSRI, versus placebo. Successful treatment of DES with SSRIs has also been demonstrated in smaller trials. The SNRI, venlafaxine, has shown some success in patients with functional chest pain. Finally, trazodone can help relieve NCCP and has also demonstrated superiority to placebo in patients with DES and the formerly-termed nutcracker esophagus.

Endoscopic Therapy for Spastic Esophageal Motility Disorders

Dilation

Endoscopic therapies for spastic motility disorders include esophageal dilation and botulinum toxin injection. As spastic motor findings on HRM can be associated with mechanical obstruction, evaluation should include a thorough endoscopic examination including biopsies to exclude eosinophilic esophagitis. However, even if an overt mechanical obstruction is not identified on endoscopy, a trial of esophageal dilation (≤20 mm) may be worth considering. It is worth noting that a previous sham-controlled, cross-over study of patients with "nutcracker esophagus" on conventional line tracing manometry demonstrated neither symptomatic nor significant manometric improvement following 54-French therapeutic bougie dilation.

Larger caliber pneumatic dilation may also be a consideration for treatment of spastic esophageal motor disorders. However, with regard to treatment of type III achalasia, pursuit of surgical myotomy is likely preferred over pneumatic dilation. In post-hoc analysis of the prospective European Achalasia study that randomized patients to pneumatic dilation versus laparoscopic Heller myotomy, the 18 patients with type III achalasia had better symptomatic outcomes when treated with Heller ($n = 8$), than with pneumatic dilation ($n = 10$) with positive outcomes in 86% vs 40%, respectively. However, another study demonstrated that benefit was reported following 30-mm (sometimes followed by 35 mm) pneumatic dilation in 14/20 patients with DES; however, an esophageal perforation also occurred. Therefore, with application of pneumatic dilation in spastic motor disorders, the consideration of lower potential for benefit (as compared with non-spastic achalasia) needs to be balanced with the small, but real, risk of perforation prior to advancing to pneumatic dilation.

Botulinum Toxin Injection

Botulinum toxin injection, which exhibits its inhibitory neuromuscular effect via cholinergic blockade, is also a potential therapeutic option. Symptomatic improvement following botulinum toxin injection into the LES +/− distal esophageal wall was reported in open-label case-series in patients with DES and/or hypercontractile esophageal disorders, as well as in a sham-controlled cross-over study in patients with DES or nutcracker esophagus. Additionally, a multi-centered, retrospective study of the safety of esophageal botulinum toxin injection found mild complications in 16% of 141 botulinum toxin injections among patients with non-achalasia spastic motility disorders. While chest pain was the most common "complication," there was report of a death following mediastinitis as the only major complication among 657 total botulinum toxin injections for all esophageal motility disorders.

However, another very important study from Mion et al. in this area was a sham-controlled, prospective trial of botulinum toxin injection for patients with type III achalasia, DES, or hypercontractile esophagus. In this study that randomized 10 patients to a sham endoscopy versus 13 patients to botulinum toxin injection and demonstrated significant symptomatic improvement in both arms, without a difference between treatment and sham. Further, HRM was repeated 3 months after randomization (in 21/23 patients) and notably, a spastic motor pattern was only observed on follow-up HRM in only 3 patients; this included resolution of the spastic HRM findings (i.e., HRM with normal motility or ineffective esophageal motility) in 75% (6/8) patients in the sham arm that completed follow-up HRM (Fig. 33.2). Therefore, while botulinum injection, or esophageal dilation, can be considered for patients with spastic motor disorders, the potential for both symptoms and manometric abnormalities to resolve with time and/or conservative management needs to be recognized. This is of particular importance prior to pursuit of invasive and irreversible interventions such as myotomy.

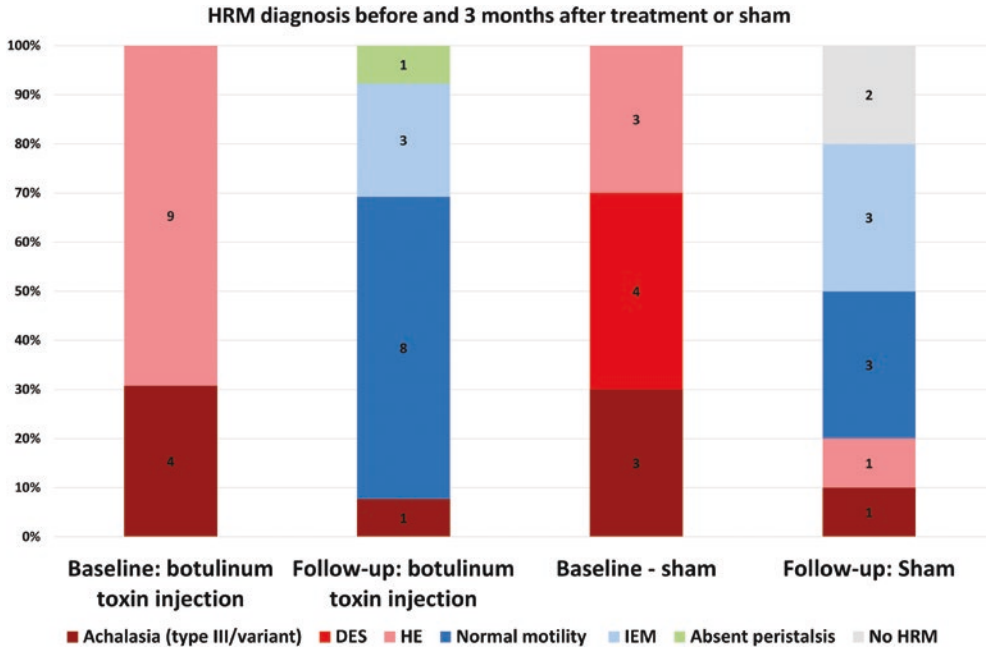

Fig. 33.2 High-resolution manometry (HRM) diagnoses at baseline and after treatment (botulinum toxin injection) or sham. "Follow-up" HRM was performed 3 months after treatment/sham. Data labels indicate the number of patients. Notably, resolution of the spastic manometric findings occurred in 6/8 patients that completed HRM in the sham arm. *IEM* ineffective esophageal motility

Surgical/Endosurgical Therapy for Spastic Esophageal Motility Disorders

Patient Selection for Surgical/Endosurgical Management

When conservative measures in the treatment of non-achalasia, primary spastic esophageal motor disorders have failed to provide sustained or meaningful relief of symptoms, more invasive measures may be considered. For patients with achalasia, especially type III achalasia, invasive measures may be considered as primary treatment. Given the known correlation between opioid medications and esophageal spastic disorders, time off opioids should be undertaken for several months before a major irreversible intervention. Even a brief history of opioid exposure or ongoing use of even mild opioid agents poses a risk of exacerbating spastic dysfunction. Myotomy can be done safely but is most valuable in symptomatic spasm patients. In the absence of symptoms, it would not be recommended to proceed with a surgical or endoscopic myotomy in most cases. Multidisciplinary care teams can help guide rational decisions.

Procedures: Laparoscopic Heller's Myotomy (LHM) and Peroral Endoscopic Myotomy (POEM)

As described for spastic esophageal disorders, LHM would include a myotomy extending at least 6 cm over the esophagus above the GE junction and at least 1.5 cm over the stomach and a fundoplication with at least a 180° closure to manage reflux. Per-oral endoscopic myotomy was originally described as a 2 cm longitudinal entry incision within the esophagus with tunnel creation followed by myotomy of the circular muscle fibers with a length of between 3 and 8 cm above the gastroesophageal junction and 2–3 cm below into the gastric area. Shorter myotomy was originally described for achalasia treatment, but when managing spastic types, longer and longer myotomies have been studied with increasing observed symptom relief noted by some interventionalists with length of myotomy. Theoretically, longer myotomy can be performed and tailored to the length of observed spastic motion in the esophagus (i.e., observed on HRM), although the benefits of longer myotomy are thought to be non-inferior in treatment of type II achalasia. There is less certainty in esophageal spastic dysfunction without achalasia.

Risks and Considerations

Myotomy carries a risk of worsening reflux, but in long myotomy some of the resultant peristaltic dysfunction, the outcome of extended myotomy is often absent peristalsis, contributes to problematic clearance of acid exposure. Thus, there may be an added risk of long myotomy to worsen total esophageal acid exposure time. When performing LHM, most surgeons can also perform a surgical fundoplication within the same session, reducing risk of long-term reflux. It

has not been possible until recently for fundoplication to be performed immediately with POEM. Recent work with transoral incisionless fundoplication and POEM has been looking at this possibility, but scant published data on the optimal patient selection for this procedure exists at this time. Not all POEM patients demonstrate abnormal acid reflux exposure, and therefore some patients will not require fundoplication. In studies of POEM without fundoplication, abnormal reflux was reported in 1 out of 5 patients studied.

Outcomes

Both LHM and POEM have effectiveness for symptomatic relief in spastic esophageal disorders and achalasia. Estremera-Arevalo and colleagues published a study showing that POEM has demonstrated an effectiveness for DES of 88% and JE of 70%. In a retrospective study of French patients at several motility centers, POEM with long myotomy (8 cm above the EGJ) was successful in improving symptoms including Eckhart score, dysphagia, regurgitation, and chest pain for patients with a variety of non-achalasia motor disorders. Response was noted at 3 months in approximately 80% and was persistent at 6 months in 63%. This study was limited by a substantial proportion of participants lost to follow-up. The benefits of POEM and LHM have been clearly demonstrated for achalasia I, II and III. Sustained relief after LHM reaches 67–85% for type I achalasia, 93% in type II, 86% in type III. For POEM, symptom improvement is similar and several meta-analyses have shown no difference in outcomes. With longer myotomy in POEM, some studies have found up to 96% of patients with improvement in type III achalasia, which is an improvement over LHM.

Cost Considerations

With respect to costs, POEM tends to be favored over LHM because it requires a shorter hospital stay, has higher clinical observed success reported in studies, a shorter operative time, and sustained symptom relief. There are only small series published regarding outcomes of relief of pain after treatment of spastic esophageal disorders, but many patients in those studies did experience pain relief. Dysphagia as measured by the Eckhart score was more reliably improved.

Concerns

The risks of POEM in spastic disorder were examined in a pooled study. Khashab et al. reported the main complications to be: pneumothorax, pulmonary embolism, capnoperitoneum, and bleeding. Rare reports of mucosectomy were listed as well. Most complications were able to be managed in real time with conservative measures. The rate of complications was 14% when being inclusive of all events, even those that required no measures of correction or change in length of stay. Other studies have quoted much lower rates of adverse events, only 7.5% in a group of 1826 subjects.

Conclusion: Surgical/Endosurgical Therapy for Spastic Esophageal Motility Disorders

Efficacy of LHM is comparable to POEM for achalasia. Efficacy is similar between methods for non-achalasia spastic esophageal disorders. POEM has known advantages in spastic disorders like type III achalasia as well as refractory non-achalasia spastic disorders like JE and DES. Ability to attain a longer myotomy appears to improve symptom outcomes. Long-term studies and more randomized studies will be needed to see if these results are maintained and to determine which methods are best to identify and control reflux long term.

Conclusions

A broad spectrum of therapeutic options that target alleviation of spastic esophageal motor activity are available for treatment of spastic esophageal motility disorders, including pharmacologic (smooth muscle relaxants), endoscopic (dilation or botulinum toxin injection), or (endo)surgical (LHM or POEM). However, it is also important to recognize that the HRM features and patterns that define these spastic disorders (i.e., type III achalasia, DES, and HE) can occur secondarily to other causes such as GERD, mechanical obstruction, or opioid use. Further, they may even carry a potential to spontaneously resolve, as evident in a sham controlled study that utilized HRM as a treatment outcome. Thus, while these treatment options can be effective, care should be taken to exclude alternative (secondary) etiologies for symptoms and "spastic" manometric abnormalities, and importantly: invasive, irreversible therapies should only be applied in carefully selected patients.

Question 1

1. **Which of the following can be an etiology for spastic motor findings on manometry?**
   A. Primary esophageal motility disorder
   B. Secondary effect of opioid use
   C. Secondary effect of mechanical obstruction
   D. Secondary effect of esophageal acid exposure
   E. All of the above

Answer: D.

Question 2

1. Which of the following was demonstrated to be more efficacious for treatment of type III achalasia than pneumatic dilation in a randomized controlled trial?
   A. Lower esophageal sphincter myotomy
   B. Botulinum toxin injection
   C. Peppermint oil
   D. Omeprazole

Answer: A.

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