

Esophageal Hypomotility and Spastic Motor Disorders: Current Diagnosis and Treatment

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Abstract Esophageal hypomotility (EH) is characterized by abnormal esophageal peristalsis, either from a reduction or absence of contractions, whereas spastic motor disorders (SMD) are characterized by an increase in the vigor and/or propagation velocity of esophageal body contractions. Their pathophysiology is not clearly known. The reduced excitation of the smooth muscle contraction mediated by cholinergic neurons and the impairment of inhibitory ganglion neuronal function mediated by nitric oxide are likely mechanisms of the peristaltic abnormalities seen in EH and SMD, respectively. Dysphagia and chest pain are the most frequent clinical manifestations for both of these dysfunctions, and gastroesophageal reflux disease (GERD) is commonly associated with these motor disorders. The introduction of high-resolution manometry (HRM) and esophageal pressure topography (EPT) has significantly enhanced the ability to diagnose EH and SMD. Novel EPT metrics in particular the development of the Chicago Classification of esophageal motor disorders has enabled improved characterization of these abnormalities. The first step in the management of EH and SMD is to treat GERD, especially when esophageal testing shows pathologic reflux. Smooth muscle relaxants (nitrates, calcium channel blockers, 5-phosphodiesterase inhibitors) and pain modulators may be useful in the management of dysphagia or pain in

SMD. Endoscopic Botox injection and pneumatic dilation are the second-line therapies. Extended myotomy of the esophageal body or peroral endoscopic myotomy (POEM) may be considered in highly selected cases but lack evidence.

Keywords Weak peristalsis · Dysphagia · Chest pain · Distal esophageal spasm · Hypercontractile esophagus · Jackhammer esophagus · Ineffective esophageal motility · High-resolution manometry · Nutcracker esophagus · Esophageal hypomotility

Introduction

Esophageal hypomotility (EH) and spastic motor disorders (SMD) are terms that have been used to define alterations in esophageal peristalsis, whether from reduction or absence or from the increased vigor or propagation velocity of esophageal body contractions. Dysphagia and chest pain are the primary clinical manifestations of both these motility disorders. Previously, using conventional linear manometry (CLM), these disorders were defined as ineffective esophageal motility (IEM), nutcracker esophagus (NE), isolated hypertensive lower esophageal sphincter (LES), and esophageal spasm [1]. In the last decade, the introduction of new technologies, such as high-resolution manometry (HRM), esophageal pressure topography (EPT), and multichannel impedance manometry (MII), has radically changed the diagnosis of EH and SMD. The identification of esophageal dysfunction biomarkers, the development of diagnostic algorithms, and the creation of a new classification of EH and SMD have all been made possible by these techniques. The Chicago Classification [2•, 3] defines these disorders as weak peristalsis, distal spasm, hypertensive peristalsis, and hypercontractile peristalsis or jackhammer esophagus. Treatment of EH and SMD is a challenge. Different therapeutic modalities exist, but their efficacy and

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safety are controversial due to the limited number of randomized clinical trials that have been conducted. In this review, we will discuss the new diagnostic criteria and the current treatment approaches for these esophageal motor disorders.

Spastic Motor Disorders

These comprise three separate manometric disorders: diffuse esophageal spasm, nutcracker esophagus, and esophageal hypercontractility or jackhammer esophagus.

Distal Esophageal Spasm

Distal esophageal spasm (DES) is a motor disorder of the esophagus that clinically presents as chest pain and/or dysphagia and is characterized by the uncoordinated contraction of the esophageal smooth muscle with manometric findings of frequent simultaneous contractions alternating with normal peristalsis. The prevalence of DES is low and, according to different case series, is estimated at between 4 and 10 % when CLM is used [4•, 5, 6] and at only 2 % in patients evaluated for dysphagia by HRM [7•].

The cause of DES is not known. Several studies have suggested that DES occurs due to loss of inhibitory ganglion neurons in the distal esophagus. The impairment of inhibitory innervation produces premature, rapid, or simultaneous contractions, as well as abnormal relaxation of the esophagogastric junction (EGJ) [8, 9]. Nitric oxide (NO) is the primary mediator of the inhibitory neurons in the esophageal myenteric plexus [10, 11]. In an experimental study, scavenging NO with recombinant hemoglobin induced simultaneous esophageal contractions and abnormal deglutitive relaxation of the EGJ in normal subjects [12]. These findings support the important role of inhibitory nitrergic tone in the pathophysiology of DES. Unfortunately, there are scarce histopathologic studies from patients with DES, and the findings are nonspecific [13, 14]. Studies with endoscopic ultrasound have shown that patients with DES have a thicker muscularis propria layer than controls [14, 15]. Also, 31–33 % of cases with DES demonstrate GERD [4•, 16].

Clinical Manifestations

Clinically, DES is characterized by intermittent chest pain or dysphagia [4•, 17]. In a recent study conducted on 108 patients diagnosed with DES using CLM, Almansa et al. [4•] found that the leading symptom was dysphagia (51 %), followed by chest pain (29 %) and heartburn (12 %). Weight loss occurred in 30 % of patients. Psychiatric disorders (depression and anxiety) were common. Interestingly, 75 % of patients were using acid-suppressive medications and 46 % were being treated with psychotropic drugs, confirming the

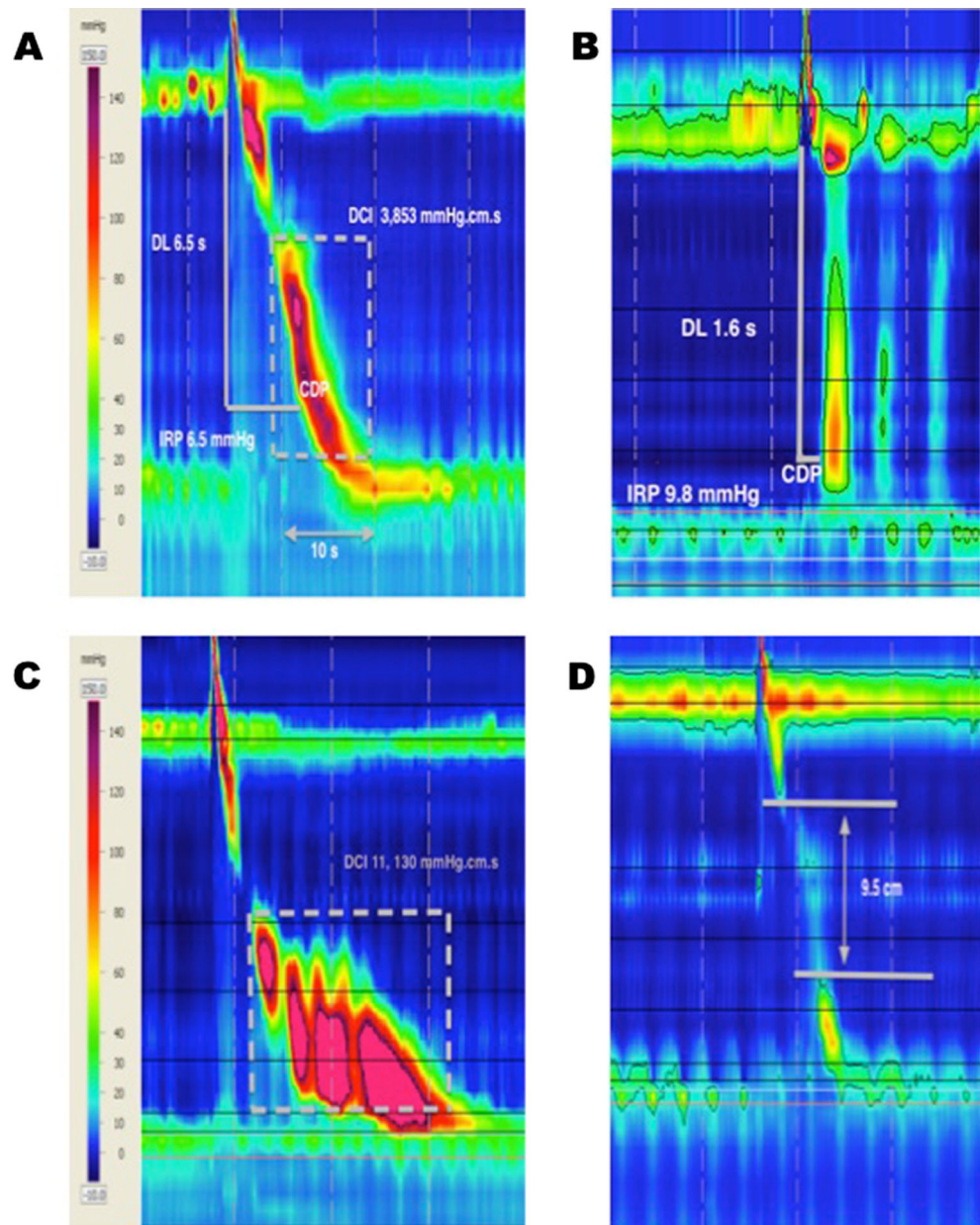
heterogeneous presentation of DES, its frequent association with GERD, and the possible role of psychological comorbidity.

Diagnosis

Esophageal Manometry Utilizing CLM, the diagnosis of DES requires the following findings: (1) simultaneous contractions in >10 % of wet swallows, (2) contraction amplitude >30 mmHg, and (3) intermittent normal peristalsis [1]. These criteria have changed significantly with the use of HRM and EPT plots. These techniques have introduced new tools that have improved the identification of DES, and they include (1) contractile deceleration point (CDP), (2) distal latency (DL), and (3) contractile front velocity (CFV). CDP is “the inflection point along the 30 mmHg isobaric contour where propagation velocity slows, demarcating the tubular esophagus from the phrenic ampulla,” DL is “the interval between upper esophageal sphincter (UES) relaxation and the CDP,” and CFV is “the slope of the tangent approximating the 30 mmHg isobaric contour between the proximal pressure at the transition zone and the CDP” [2•, 18, 19] (Fig. 1a). Utilizing these metrics, Pandolfino et al. [7•] analyzed 1070 patients presenting with esophageal symptoms. Patient classification was based on the CFV and DL in those presenting with rapid contractions (CFV >9 cm/s and DL >4.5), premature contractions (CFV <9 cm/s and DL <4.5 s), and with rapid, premature contractions (CFV >9 cm/s and DL <4.5 s). Using these parameters, the authors found only 24 patients (2.2 %) with a DL <4.5 s, all of whom had chest pain or dysphagia. Eighteen of those patients were diagnosed with achalasia, and DES was established in the remaining 6. Two of those six patients presenting with DES had premature contractions, and four had rapid and premature contractions. There was no clinical basis for diagnosing DES in any of the patients that presented with both rapid contractions and no premature contractions. With these results, the authors showed that the finding of simultaneous (rapid) contractions corresponded to a very heterogeneous group of patients, the majority of whom did not present with DES. Therefore, the identification of patients with this disorder improved through the presence of premature contractions defined by a DL <4.5 s. The authors proposed that DES diagnosis with EPT requires the presence of at least two premature contractions (DL <4.5 s) and normal EGJ relaxation [mean integrated relaxation pressure (IRP) <15 mmHg] (Fig. 1b).

Barium Swallow “Corkscrew esophagus” or “rosary bead esophagus” is the finding in the barium swallow used to describe the patient with DES, but it is rarely observed in patients with a manometric diagnosis of DES, and usually corresponds to spastic achalasia [20, 21]. Almansa et al. [4•] recently found that abnormal peristalsis was identified through esophagogram in 61 % of the patients evaluated. However, the

Fig. 1 (a) Esophageal pressure topography (EPT) from a healthy volunteer showing normal integral resting pressure (IRP), distal latency (DL), and distal contractile integral (DCI). (b) EPT from a patient with distal spasm: normal IRP and short DL. (c) EPT from a patient with jackhammer esophagus: normal IRP, normal DL, and DIC >8000 mmHg s cm. (d) Weak peristalsis: EPT of a swallow with a large break in the mid-esophagus



classical corkscrew esophagus was noted in only 4 % of the patients with DES.

Endoscopy and 24-h Esophageal pH Monitoring Upper GI endoscopy is of limited value in the diagnosis of DES. However, it is very useful for excluding mechanical causes of dysphagia such as stenosis, rings, neoplasia, or peptic esophagitis and eosinophilic esophagitis. Endoscopic findings of tertiary contractions, esophageal dilation, and resistance to the passage of the endoscope in the EGJ may suggest a spastic disorder of the esophagus or achalasia. In 101 patients with DES that underwent upper endoscopy, Almansa et al. [4•] found esophagitis in 25 % of cases hiatal hernia in 32 %, Schatzki ring in 14 %, and epiphrenic diverticulum in 5 %.

Esophageal pH monitoring is indicated in the evaluation of patients with DES that have chest pain, heartburn, and regurgitation, especially to rule out the presence of abnormal acid reflux. At least 38 % of patients with DES are diagnosed with GERD by a combination of upper endoscopy and 24-h pH monitoring [4•].

Hypertensive Peristalsis (Nutcracker Esophagus)

Nutcracker esophagus (NE) is a motor disorder found in patients with chest pain and dysphagia and is characterized by hypertensive, but normally propagated, contractions [1, 22]. Even though this disorder was described more than 30 years ago [23], there is still much controversy as to whether

NE is a true esophageal motor disorder, a manometric marker of noncardiac chest pain (NCCP), or an epiphenomenon of GERD. It occurs in 48 % of the patients with NCCP and coexists with GERD in 33–77 % of the cases [16, 24•].

The pathophysiology of NE is not very clear. Studies combining esophageal manometry and high-frequency ultrasound have shown the presence of hypertrophy of the muscularis propria in patients with hypertensive contractions [15, 25]. Asynchrony between the circular and longitudinal esophageal muscle contractions has also been demonstrated in patients with NE [25, 26]. Cholinergic stimulation with edrophonium in healthy patients induces asynchrony in the contraction of both muscle layers of the esophagus, and this condition can be reversed with atropine [27, 28]. These findings suggest that an excessive cholinergic tone may explain the vigorous contractions seen in NE.

Clinical Manifestations

NE is more frequent in women in the sixth decade of life. The most common symptoms are chest pain and dysphagia. In a recent study that included 115 patients presenting with manometric NE criteria, Lufitano et al. [24•] found that chest pain and dysphagia occurred in 31 and 21 % of subjects, respectively. GERD symptoms were very common. Heartburn occurred in 51 % of patients, 77 % had a previous history of GERD, and 78 % were treated with acid suppressive medications. GERD was demonstrated through esophageal testing in at least 35 % of the patients. Psychological comorbidity was present in 24 % of the patients with NE and irritable bowel syndrome coexisted in 15 % of the patients, respectively. This study confirmed that NE is associated with GERD, psychological comorbidity, and other functional gastrointestinal disorders.

Diagnosis

Manometric diagnosis of NE has changed over time. Using CLM, NE was originally defined by the presence of a mean amplitude greater than 180 mmHg (corresponding to more than 2 standard deviations above the normal values) in the distal third of the esophagus [1]. This cutoff level was later increased to 260 mmHg (more than 4 SDs above the normal) for the purpose of improving specificity and identifying patients with dysphagia and chest pain more often and patients with GERD less often [29]. Patients with NE generally have normal LES pressure, and in some cases, hypertensive LES defined by a resting pressure >45 mmHg can coexist [1, 3].

HRM and EPT plots have introduced the distal contractile integral (DCI) as a new tool to improve characterization of esophageal peristaltic vigor [3]. DCI represents the volume of the distal contraction using an isobaric contour of 20 mmHg, and it is calculated by multiplying the integral of the

contraction amplitude (mmHg) in the distal esophagus times the duration of the contraction (s) times the length of the distal esophageal segment (cm) [2••, 3] (Fig. 1a). In 75 healthy volunteers, Pandolfino et al. [3] found that the median (IQR) DCI was 2416 mmHg s cm, and a DCI value >5000 mmHg s cm (95th percentile of normal distribution) was considered abnormal. This DCI value of 5000 mmHg s cm corresponds to NE in CLM. Furthermore, they found that a value of DCI >8000 mmHg s cm was never encountered in healthy volunteers. Thus, hypertensive peristalsis was defined as the presence of a mean DCI >5000 mmHg s cm and does not include any swallow with a DCI >8000 mmHg s cm.

Esophageal Hypercontractility (Jackhammer Esophagus)

Jackhammer esophagus (JE) corresponds to an extreme phenotype of the motor disorders with hypertensive peristalsis. Using EPT plots, Roman et al. [30, 31••] defined JE as the presence of at least one contraction with DCI >8000 mmHg s cm in the context of normal peristalsis propagation (normal CFV and normal DL) (Fig. 1c). It is a rare disorder that presents in 4.1 % of the patients referred for manometric evaluation in tertiary referral centers. Dysphagia, chest pain, and GERD symptoms are the most common of its varied clinical manifestations. Interestingly, patients with JE can present with different hypercontractility patterns in the EPT plots: single or multi-peaked contractions. The patterns with multi-peaked contractions were associated with EGJ obstruction. There were no clinical differences between these hypercontractility patterns [31••].

The pathophysiology of this disorder is unknown. An excessive cholinergic stimulation, like that seen in hypertensive peristalsis, appears to be the mechanism responsible for the hypercontractile state.

Progression to Achalasia

EGJ outflow obstruction (IRP >15 mmHg) can be found in patients with DES and JE. Case series and case reports have shown progression of DES and NE to achalasia [32–34]. Fontes et al. [32] found that in 35 patients previously diagnosed with DES by CLM, 14 % progressed to achalasia at a mean follow-up of 2.1 years. However, this is a very limited evidence to confirm that SMD can progress to achalasia. Further studies with HRM and EPT plots are necessary to clarify the natural history of SMD.

Treatment of Spastic Motor Disorders

Different therapeutic modalities have been tried in SMD management, but few randomized clinical trials have been conducted. Most results are based on case series, case reports, or expert opinion.

Pharmacologic Treatment

Short- or long-acting nitrates, calcium channel blockers, anticholinergic agents, and 5-phosphodiesterase inhibitors have been employed because of their relaxing effect on smooth muscle [35–37]. Tricyclic antidepressants and serotonin reuptake inhibitors have been used as visceral pain modulators [37–44]. The majority of these studies were directed towards management of patients with chest pain and not necessarily NE or DES [10, 37, 39].

Nifedipine and diltiazem have shown limited efficacy in chest pain and dysphagia management in randomized studies when compared with placebo [45–48], and headache is a frequent adverse effect. 5-Phosphodiesterase inhibitors, such as sildenafil, have shown some effectiveness in improving symptoms and manometric parameters [49–51].

In a population of patients treated for NCCP, there was improvement in 52, 50, and 63 % of the cases with the use of imipramine, venlafaxine, and sertraline, respectively [40–42, 52]. The manometric characteristics were not evaluated after the interventions in any of the studies. Trazodone has been shown to be superior to placebo in overall improvement and chest pain [43]. A great limitation of these drugs is the high frequency of adverse effects, resulting in treatment suspension by patients. Therefore, visceral pain modulators should be started at low doses and gradually increased on a weekly basis [53].

Due to the possible overlap of NE and DES with GERD, proton pump inhibitors should be tried first, especially if abnormal acid reflux is demonstrated with pH monitoring [54, 55].

Endoscopic Treatment

Endoscopic injection of botulinum toxin (BTX) is a treatment for achalasia [56, 57] and has been tried in DES and JE due to its effect on cholinergic transmission as a neuromuscular blocking agent. In studies with no controls, BTX injection has improved chest pain and dysphagia in patients with spastic motor disorders [58–60]. In a recent randomized clinical trial on 22 patients with DES and NE, BTX injection was superior to saline injection in controlling dysphagia, but not in reducing chest pain [61]. The BTX injection protocol has not been standardized, and injections have been used in the EGJ or the distal third of the esophagus. Randomized clinical trials are required in order to examine the efficacy of BTX in spastic disorders of the esophagus.

Pneumatic dilation has been employed in the treatment of spastic disorders of the esophagus with some reports showing favorable results [62], but it is not known if the reported improvement was due to the inclusion of patients with achalasia.

Peroral endoscopic myotomy (POEM) has been introduced for treatment of achalasia [63–65] and has recently been used in isolated cases of DES and JE with some success [66, 67, 68, 69]. The medium-term and long-term results of this technique are not known and hence should be employed only in research protocols.

Surgical Treatment

Long myotomy that extends from the EGJ and along the esophageal body with complete or partial fundoplication has been tried in cases of DES and JE [70, 71]. Relief of both chest pain and dysphagia has been described in 60 to 80 % of treated cases [70, 72]. However, there is a lack of control group, standardized symptom evaluation, and objective measurement of gastroesophageal reflux after surgery. Therefore, extended myotomy may be considered in cases of persistent pain or dysphagia that is refractory to other treatments.

In summary, we recommend the following treatment approach for spastic disorders of the esophagus (Table 1):

1. First-line treatment: (a) acid suppressive therapy with PPIs in patients with associated GERD demonstrated by endoscopy or 24-h ambulatory esophageal pH; (b) smooth muscle relaxants such as nitrates, calcium channel blockers, or sildenafil in patients without evidence of GERD; and (c) Pain modulators such as tricyclic antidepressants, serotonin reuptake inhibitors, or trazodone for the management of patients with chest pain as the leading symptom.
2. Second-line treatment: patients who do not respond to first-line approach can be treated with endoscopic BTX injection or esophageal dilation. A temporary or partial response may be an indication for repeat therapy.
3. Third-line treatment: rarely extended myotomy either by surgery or POEM for treatment-refractory spastic disorders.

Esophageal Hypomotility

Esophageal hypomotility disorders are characterized by a decrease in the vigor of distal esophageal contractions associated with abnormalities of esophageal transit. IEM is the most widely used term for these disorders identified by CLM [1]. Their clinical presentation is dysphagia, and they are frequently associated with GERD. IEM is also seen in other systemic conditions which affects the esophagus, such as scleroderma, diabetes mellitus, hypothyroidism, etc [73, 74].

The pathophysiology of IEM is not yet defined. An estimated 21 to 49 % of patients presenting with IEM also have

Table 1 Treatment options in spastic motor disorders and esophageal hypomotility

Spastic motor disorders (DES, JE, NE)	
First-line therapy	PPIs in concurrent GERD Nitrates Calcium channel blockers (nifedipine, diltiazem) 5-Phosphodiesterase inhibitors (sildenafil) Pain modulators (low-dose antidepressants)
Second-line therapy	Botulinum toxin injection Pneumatic dilation
Third-line therapy	Extended myotomy (surgery, POEM)
Esophageal hypomotility	
	Manage GERD (PPIs, antireflux procedure) Prokinetics?

DES distal esophageal spasm, *JE* jackhammer esophagus, *NE* nutcracker esophagus, *PPIs* proton pump inhibitors, *POEM* peroral endoscopic myotomy

associated GERD [75, 76]. This association is more frequent in the presence of erosive esophagitis [77, 78]. Some studies have shown that esophageal hypomotility may be reversible in acute esophagitis, but not in chronic esophagitis [78], suggesting that chronic inflammation may cause permanent damage to esophageal motor function. Experimental studies in animals and humans have shown that proinflammatory cytokines spread throughout the esophageal wall in esophagitis and reduce esophageal contractility by decreasing the release of acetylcholine from the neurons of the myenteric plexus into the circular muscle layer [79–82].

Manometric Diagnosis

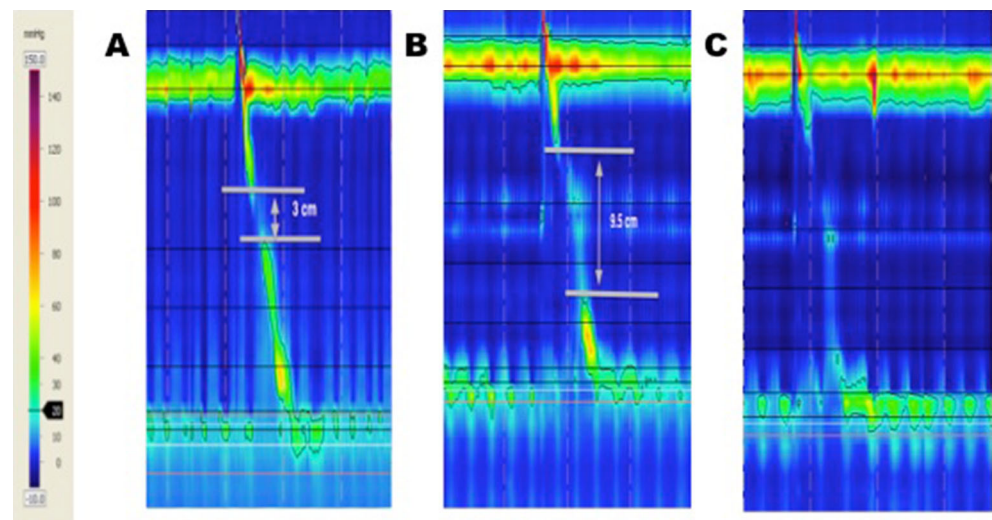
Manometric diagnosis of IEM is established by the presence of contractions in >30 % of wet swallows with any of the following characteristics: (1) peristaltic contractions with an amplitude of

<30 mmHg, (2) simultaneous contractions <30 mmHg, (3) failed peristalsis (the peristaltic contraction does not cross the entire length of the distal esophageal body) (Fig. 2), or (4) absent peristalsis [1]. The contraction amplitude criterion of <30 mmHg was established based on its correlation with disorders in esophageal transit observed in videofluoroscopy [77, 83]. Subsequently, using combined esophageal impedance and conventional manometry, Blonski et al. [84] demonstrated that the presence of >50 % of contractions with <30 mmHg identified patients with abnormal esophageal transit and symptoms like heartburn and dysphagia more frequently.

Manometric diagnosis of esophageal hypomotility with HRM and high-resolution impedance manometry (HRIM) has recently been defined. Four tools of EPT plots have been shown to be useful for defining EH: (1) the presence of frequent small or large breaks in the 20-mmHg isobaric contour (IBC) at the distal esophageal pressure troughs, (2) DCI <450 mmHg s cm, (3) measurement of intersegmental trough (IST) length or transitional zone defects, and (4) proximal latency (PL). In asymptomatic volunteers and patients with nonobstructive dysphagia, Roman et al. [85••] showed that the presence of breaks in the 20-mmHg IBC was associated with incomplete bolus transit (IBT). Additionally, they found that the presence of >20 % of large breaks (>5 cm) or >30 % of small breaks (2–5 cm), but not failed peristalsis, occurred significantly more frequently in patients with nonobstructive dysphagia.

These manometric findings were included in the Chicago Classification for defining esophageal disorders with weak peristalsis [2••]. Xiao et al. [86] recently evaluated the use of HRM to define IEM in a case series of 150 patients with nonobstructive dysphagia or GERD. They found that by using a combination of the Chicago Classification criteria (weak peristalsis with large or small breaks and frequent failed peristalsis localized in the middle and distal esophageal pressure troughs), there was a positive percent agreement of 78.6 % and a negative percent agreement of 92 % with IEM.

Fig. 2 (a) Hypotensive peristalsis with small break (between 2 and 5 cm). (b) Hypotensive peristalsis with a large break (>5 cm). (c) Failed peristalsis



They also found that a DCI cutoff value of <450 mmHg s cm was optimal for characterizing ineffective esophageal swallows. The agreement between IEM defined by conventional manometry and a DCI <450 mmHg s cm found in >5 swallows in HRM was even better (85.7 % positive percent and 92.3 % negative percent agreement). More recently, Kumar et al. [87•] evaluated IST and PL as possible esophageal hypomotility markers in 110 patients with GERD, 74 patients without GERD, and 15 healthy controls. Using a 20-mmHg IBC, IST length was defined as “the vertical distance from the distal extent of the proximal striated muscle to the proximal extent of the smooth muscle contraction segment.” The IST was considered as extended if it exceeded 20 % of the total esophageal length in ≥ 30 % of wet swallows. PL was defined as the time duration from the onset of UES relaxation to the most proximal point of the smooth muscle contraction segment. PL was considered prolonged if it exceeded 4 s in >50 % of wet swallows. They found that IST and PL were longer in the GERD patients than in the non-GERD patients and controls. Extended IST was more frequent in the GERD group (44.5 %) compared with the non-GERD patients (27 %) and controls (26.7 %). Patients with Barrett’s esophagus had the highest prevalence of extended IST (56 %). Prolonged PL followed similar trends. Interestingly, peak and mean contraction amplitudes were lower in patients with GERD and more frequent in those with extended IST. The findings of this study suggest that the identification of extended IST and prolonged PL with HRM supports EH as a mechanism for explaining esophageal symptoms, especially in patients with GERD.

Treatment

Due to the frequent association of IEM with GERD, acid-suppressive therapy or an antireflux procedure is indicated in patients with objective signs of reflux (endoscopic esophagitis or abnormal 24-h pH testing). Different studies have demonstrated that IEM is not a contraindication for antireflux surgery; it does not have an impact on the outcome of the surgery and does not require tailoring of surgical treatment. In the majority of patients, IEM is not corrected with PPI treatment or with fundoplication, regardless of the type of procedure employed (Nissen or Toupet) [88–91].

Unfortunately, there are few treatment options for patients with EH and dysphagia. Different prokinetic agents have been shown to increase contraction amplitude and improve esophageal transit in normal subjects and in patients with EH. However, its usefulness in the control of dysphagia is questionable [92, 93]. Procholinergic agents, dopamine D2 antagonists, 5HT4 serotonin, and prokinetic agents have been tried in an attempt to improve dysphagia in patients with EH [92, 94–96].

Conclusions

The diagnosis of EH and SMD has changed significantly with the introduction of HRM and EPT plots. The Chicago Classification has established new diagnostic criteria for DES, hypertensive peristalsis, JE, and weak and failed peristalsis. These esophageal motor disorders are frequently associated with GERD, and the objective demonstration of pathologic reflux is an indication for acid-suppressive therapy. First-line treatment in SMD includes the use of smooth muscle relaxants for dysphagia management and pain modulators for the treatment of chest pain. BTX injection and pneumatic dilation are both second-line therapy modalities. Extended myotomy performed by surgery or POEM is reserved for cases that are refractory to other therapies.

Compliance with Ethics Guidelines

Conflict of Interest Miguel A. Valdovinos, Monica R. Zavala-Solares, and Enrique Coss-Adame declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors’ research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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