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The Relevance of Spastic Esophageal Disorders as a Diagnostic Category

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Abstract

Purpose of Review This review addresses the similarities and differences between the spastic esophageal disorders, including jackhammer esophagus, distal esophageal spasm (DES), and type III (spastic) achalasia. The pathophysiology, diagnosis, and treatment of each separate disorder are discussed herein, with an emphasis on overlapping and discordant features.

Recent Findings The Chicago Classification is a hierarchical organizational scheme for esophageal motility disorders, currently in its third iteration, with direct impact on the definitions of these three disorders. Complementary diagnostic tools such as impedance planimetry and novel manometric parameters continue to evolve. The suite of potential treatments for these disorders is also expanding, with progressive interest in the role of peroral endoscopic myotomy alongside established pharmacologic and mechanical interventions.

Summary Although jackhammer esophagus, distal esophageal spasm, and type III achalasia frequently overlap in terms of their clinical presentation and available management approaches, the divergences in their respective diagnostic criteria suggest that additional study may reveal additional mechanistic distinctions that lead in turn to further refinements in therapeutic decision-making.

Keywords Hypercontractility · Nutcracker · Achalasia · Manometry · Esophageal spasm · Dysmotility

Abbreviations

DES	Distal esophageal spasm
CC	Chicago Classification
HRM	High-resolution manometry
DCI	Distal contractile integral
LES	Lower esophageal sphincter
IRP	Integrated relaxation pressure
UES	Upper esophageal sphincter
DL	Distal latency
CDP	Contractile deceleration point
GERD	Gastroesophageal reflux disease
EoE	Eosinophilic esophagitis
EGJ	Esophagogastric junction
EGJOO	Esophagogastric junction outflow obstruction
PFV	Pressurization front velocity
CFV	Contractile front velocity
PPI	Proton pump inhibitor
FLIP	Functional luminal imaging probe
EUS	Endoscopic ultrasound
HM	Heller myotomy
POEM	Peroral endoscopic myotomy

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Introduction

As a category, spastic esophageal disorders are typically thought to comprise three entities: jackhammer esophagus, distal esophageal spasm (DES), and type III (spastic) achalasia. The presumed convergences among them in pathophysiology and clinical management exist alongside clear divergences in the formal manometric criteria with which each diagnosis is associated. Are these distinct disorders, or do they exist along a common spectrum? What do we mean when we talk about "spasm"? Understanding the similarities and differences among these diagnoses has potential bearing on the course of future diagnostics and therapies. Herein, we review the history, pathophysiology, diagnosis, and treatment of these three disorders, with the aim of clarifying the utility of their mutual association.

Manometric Definitions

In general, spastic esophageal disorders are thought to be characterized by increased contractile vigor. The primary metric by which this vigor is signaled, however, varies by diagnosis. The Chicago Classification (CC), a hierarchical organizational scheme for esophageal motility disorders currently in its third iteration, has progressively revised the high-resolution manometry (HRM) parameters of particular relevance in identifying these disorders. The first and second versions of this classification scheme were published in 2009 and 2012 respectively; its third and most recent iteration (labeled by its authors as CC version 3.0) was published in 2015.

In CC version 3.0, distal contractile integral (DCI) is defined as the product of the amplitude, duration, and length (mmHg·seconds·cm) of the distal esophageal contraction exceeding 20 mmHg from the transition zone to the proximal margin of the lower esophageal sphincter (LES). Integrated relaxation pressure (IRP) is defined as the average pressure within the 4 s of maximal deglutitive relaxation within the 10-s window beginning at the relaxation of the upper esophageal sphincter (UES) and in reference to a baseline gastric pressure. Distal latency (DL) is defined as the interval from upper esophageal sphincter (UES) relaxation to the contractile deceleration point (CDP, defined as the inflection point where propagation velocity slows within 3 cm of the proximal border of the LES) [1••].

With regard to these individual parameters, jackhammer esophagus is currently defined as ≥ 20% of swallows with a DCI greater than 8000 mmHg·s·cm. DES is currently defined as ≥ 20% premature contractions, which are defined as those with a DL less than 4.5 s. Type III achalasia is currently defined as a median IRP greater than 15 mmHg, premature contractions with ≥ 20% of swallows, and no swallows demonstrating normal peristalsis. Type III achalasia overlaps with DES in that both criteria include DL less than 4.5 s, but as distinct from achalasia, DES and jackhammer esophagus are both characterized by a normal median IRP [1••, 2].

The definitions of spastic esophageal disorders have changed with the transition from conventional manometry to HRM, and more recently, as the CC has evolved from its first through third iterations. The history of these changes is worth bearing in mind, as previous manometric features of spasm may have been deemphasized or overwritten. For instance, multi-peaked contractions are a common finding on conventional manometry in patients with esophageal hypercontractility, and in retrospect particularly with jackhammer esophagus. With the advent of DCI, however, interpretive focus has in general shifted away from contractile morphology [3]. The manometric diagnosis of nutcracker esophagus, incorporated into the first and second versions of the CC, defined by a mean DCI between 5000 and 8000 mmHg·s·cm, and at one time subdivided into three discrete subtypes, has been removed completely from the most recent classification [1••, 4]. Hypercontractile esophagus is now synonymous with jackhammer esophagus, with the definition now including LES contraction in the aggregate DCI measurement and an acknowledgement of the entity's potential occurrence secondary to gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), or EGJ outflow obstruction (EGJOO) [1••].

By conventional manometry, DES had been defined as the presence of ≥ 20% swallows with simultaneous contractions with a minimum amplitude of 30 mmHg; with the transition to HRM, and in particular the first version of the CC, attention shifted toward contractile speed, and specifically the concept of pressurization front velocity (PFV, defined as the slope between the distal margin of the transition zone and the proximal margin of the EGJ at the 30 mmHg isobar). Patients deemed to have rapidly propagated pressurization were further subdivided into categories of spasm and compartmentalized esophageal pressurization. New metrics were introduced in the second version of the CC, including CDP, DL, and contractile front velocity (CFV), the latter having been deemphasized subsequently in CC version 3.0 given its relative lack of specificity for spasm [4].

The characterization of esophagogastric junction (EGJ) relaxation has been refined with the transition to HRM. Esophageal shortening associated with peristalsis and accentuated by spasm could lead to diagnostic uncertainty regarding the adequacy of EGJ relaxation, uncertainty that was mitigated with improved localization of this landmark by HRM [5]. It was the 2012 version of the CC that formalized the division of achalasia into three subtypes, with type III achalasia supplanting the prior concept of vigorous achalasia [4]. Relative to conventional manometry, HRM likely reduces the risk of miscategorizing type II versus type III achalasia by facilitating a clearer visual distinction between panesophageal pressurization and distal spasm [5]. In CC version 3.0, type III achalasia was also carefully distinguished from EGJ outflow obstruction with preserved peristalsis, the latter potentially indicative of early or incompletely expressed achalasia, sliding or paraesophageal hiatal hernia, vascular obstruction of the distal esophagus, infiltrative disease, or tumor [1••].

Pathophysiology

Peristalsis in the esophageal smooth muscle is regulated by inhibitory (primarily nitronergic) and excitatory (primarily cholinergic) neurons [6]. With regard to pathophysiology, the major distinction in the presumptive models for the spastic esophageal disorders is between jackhammer esophagus, which is thought to be related to excess cholinergic drive, and DES and type III achalasia, which are both thought to be related to impaired inhibition [6–8].

The density of inhibitory ganglia in the distal esophagus increases with increasing proximity to the lower esophageal sphincter. This neural gradient facilitates the appropriate timing and coordination of peristalsis in the distal esophagus after initiation of swallowing. Accordingly, premature contractions characterized by reduced DL are thought to be a manifestation of impaired inhibition leading to an inappropriately early contraction of the distal esophagus [6]. The presumed distinction between DES and type III achalasia, then, is whether or not this impairment also affects the relaxation of the EGJ. By contrast, the understanding of hypercontractile esophagus as a function of excess cholinergic stimulation is suggested by evidence of temporal discoordination of contractions in the circular and smooth muscle of the esophagus and the inducibility and reversibility of this discoordination by edrophonium and atropine, respectively [8, 7].

Spastic esophageal disorders may also be observed in conjunction with separate esophageal processes, however, with potential implications for both pathophysiology and management. For instance, multiple studies have shown that EGJOO induced by mechanical means can lead to hypercontractility of the esophageal body [9–10]. Gyawali et al. showed that patients with EGJOO developed a motor pattern with multipeaked contractions, increased distal esophageal amplitude, and increased contraction duration [10]. GERD can also coincide with spastic disorders of the esophagus. Experimental evidence suggests that esophageal acid perfusion can cause esophageal spasm; similarly, patients with jackhammer esophagus and concomitant reflux esophagitis have demonstrated improvement of spasm when treated with proton pump inhibitors (PPI) [11, 12, 13].

With regard to EoE, manometric abnormalities have been noted from 4 to 87% of patients, depending on the case series reviewed [14]. In a series of 21 patients with EoE, Martin et al. suggested that panesophageal pressurization was the most frequent manometric abnormality noted in the setting of EoE and, when present, was associated with the risk of bolus impaction [15]. A separate retrospective review of just over 500 cases of achalasia found that < 1% had evidence of concomitant EoE. Of these, the authors noted that manometric changes after steroid treatment were inconsistent and that long-term response to symptomatic intervention targeted toward each of these entities tended to be poor [16].

Diagnosis

While each of the spastic esophageal disorders can have varied presentations, they do share some common symptomatic features. All three can present with dysphagia, heartburn, chest pain, and regurgitation. Jackhammer esophagus and spastic achalasia patients often have intermittent chest pain or dysphagia [17]. A study by Kristo et al. showed that in 30 patients with jackhammer esophagus, dysphagia and chest pain were noted in 53.5 and 40%, respectively. Dysphagia was associated with DCI scores, hypercontractile swallows, and maximum DCI swallows [18]. Another retrospective study considering a cohort of 32 patients with untreated achalasia found that, of the 5 patients with type III achalasia, 100% experienced dysphagia and chest pain [19]. A study by Almansa et al. showed that common symptoms in 108 patients with DES included dysphagia (51%), chest pain (29%), and heartburn (12%) [20].

The diagnosis of spastic esophageal disorders has involved manometry, imaging, and endoscopy, among other testing modalities that have evolved over time. As these entities are defined with a categorization scheme rooted in HRM parameters, manometry is generally regarded as essential to the diagnosis of spastic esophageal disorders. That being said, a variety of old and new technologies may be used to provide complementary information in the context of suspicion for a spastic disorder. Additionally, novel interpretations of manometric data are being actively elaborated for the purposes of meaningful clinical subcategorization.

Barium esophagram traditionally has been used to aid in the characterization of each of these disorders, but the diagnostic yield of this modality is variable. In a study by Finnerty et al., 100 patients were evaluated by barium esophagram and HRM, and using HRM as the gold standard, barium esophagram had an overall sensitivity of 88% and specificity of 35% for detecting esophageal dysmotility of any type [21]. With particular attention to achalasia, sensitivity was 100%, but specificity remained low at 32%. In achalasia, typical barium esophagram findings include esophageal dilation, incomplete LES relaxation, stasis of contrast in the esophagus, and tertiary contractions [22–24]. Jackhammer esophagus may present with normal or non-specific barium esophagram findings, such as interrupted primary peristalsis or variable tertiary (non-propulsive) contractions [21]. Tertiary contractions are simultaneous contractions that may represent non-peristaltic esophageal motor function and can be seen in patients with and without spastic disorders; in isolation, tertiary contractions rarely signify a motor disorder [25]. Barium esophagram findings in DES tend to be similarly non-specific; in a study of 108 patients with a diagnosis of DES, 61% had an abnormal esophagram, but the classically associated findings of a corkscrew or rosary bead appearance were noted in only 4% of patients in this cohort [20, 21].

Upper endoscopy is performed routinely in the evaluation of suspected spastic esophageal disorders to exclude competing/concomitant structural or mucosal abnormalities that might correlate with a patient's symptoms. Such abnormalities might include mechanical obstruction, esophagitis, epiphrenic diverticula, or biopsy evidence of esophageal eosinophilia [26]. While achalasia is not typically associated with endoscopic abnormalities, abnormal contractions or

dilation of the esophageal body, retained secretions, and increased resistance at the EGJ may be observed [27].

Certain refinements of standard manometric indices have recently been proposed, including distinctions between pre-peak and post-peak DCI with attention to the morphology of the contractile wave. A 2017 study by Xiao et al., which evaluated 71 healthy controls with HRM and divided the DCI analysis into time-controlled pre-peak and post-peak phases, found that the post-peak phase had a relatively greater contribution to contractile effort [28]. A subsequent study by the same group found that, among 38 patients with jackhammer esophagus, there was a higher ratio of post-peak DCI to pre-peak DCI in comparison with asymptomatic controls, and that there was a trend toward significance in the association between this ratio and dysphagia symptom severity. On this basis, the authors conjectured that abnormalities in post-peak peristalsis may have an outsized contribution to dysphagia symptoms in patients with jackhammer esophagus [29]. Further study is needed, but this more granular analysis of contractile activity has been proposed as a means of resolving the otherwise incomplete correlation between clinical symptoms and peristaltic amplitude and morphology, with attention to the likely underlying heterogeneity of neuromuscular aberrancies involved [30–32].

Impedance planimetry, a method for assessing luminal compliance, has been used as a complementary modality in the diagnosis of various esophageal disorders. The functional luminal imaging probe (FLIP) is a catheter-based impedance planimetry probe that recently has become commercially available and that has demonstrated diagnostic utility in a variety of settings [33]. It can confirm the presence of EGJOO or achalasia, for instance, by demonstrating reduced distensibility at the EGJ. More recently, enhanced analytic methods for contractility patterns observed through impedance planimetry of the esophageal body have led to FLIP topography, a complementary method for characterizing esophageal motility disorders. In a study of 145 patients with non-obstructive dysphagia, Carlson et al. demonstrated that FLIP topography could serve as a useful adjunct to HRM in the diagnosis of motility disorders, including identifying subtle abnormalities in patients with normal manometric findings. Comparing findings between HRM and FLIP topography highlights the occasionally blurred lines separating the spastic esophageal disorders; of 12 patients with HRM findings of type III achalasia, 10 had FLIP topography findings of spastic achalasia and 2 of EGJOO, whereas of 3 patients with HRM findings of jackhammer esophagus, all 3 had FLIP topography findings of spastic achalasia [34•, 35].

Additional complementary studies include the use of HRM catheters with impedance sensors to assess bolus transit, potentially yielding additional information regarding the functional significance of observed manometric abnormalities in spastic esophageal disorders [36–38]. Computed tomography scans and endoscopic ultrasound (EUS) can demonstrate esophageal thickening as a potential correlate of esophageal spasm [20, 39]. This thickening tends to be concentric, in contrast with tumors, which both of these imaging modalities can also be used to exclude, particularly when hypercontractility or outflow impairment is suspected to be secondary to mechanical obstruction [39].

Treatment

Despite differences in the spastic esophageal disorders' manometric definitions, common treatment approaches are often applied across these three disease categories. Pharma cotherapy is often employed in jackhammer esophagus and DES, while mechanical interventions including injections and myotomy have been considered in all cases.

Medications have been used to treat all three spastic disorders but unfortunately have little to no role in achalasia therapy. Smooth muscle relaxants, such as calcium channel blockers and nitrates, are used to reduce LES pressure and contraction amplitude [40]. Nitrates have been shown to prolong DL and decrease distal contraction amplitude in patients with DES and may improve chest discomfort [41]. To our knowledge, however, there have been no controlled trials with nitrates in patients with DES or jackhammer esophagus. Phosphodiesterase-5 inhibitors block degradation of nitric oxide to prolong smooth muscle relaxation in DES and jackhammer esophagus but are associated with high costs and the risk of side effects of dizziness and headaches [42, 43, 44]. One small series of eight patients noted that peppermint oil eliminated simultaneous contractions in DES but mitigated chest pain symptoms in only two patients [45]. In the context of a case report, positive benefit has also been noted with biofeedback for DES [46]. It should be noted that PPIs are thought to reduce symptoms of spastic esophageal disorders when there is an overlap with untreated GERD.

Injections of botulinum toxin have been used in jackhammer esophagus, DES, and type III achalasia, though again with differences in efficacy across these disorders. Botulinum toxin injections at the level of the EGJ have been shown to be effective in achalasia, though effects are generally temporary and wane over time [47]. A meta-analysis comparing nine studies involving botulinum toxin injection showed that after one session, symptomatic improvement was 78.7% at 1 month, 70% at 3 months, 53.3% at 6 months, and 50.6% after 12 months of follow-up [47]. Pneumatic dilation and myotomy, as more definitive means of disrupting the LES, have been found to be more effective treatment for achalasia than botulinum toxin injection [48]. It is worth noting, however, that response rates to certain therapies vary by achalasia subtype; type III achalasia, for example, has a relative poor likelihood of success with pneumatic dilation in comparison

with type II achalasia and in comparison with surgical myotomy [49]. Of course, the invasiveness and complication rates associated with botulinum toxin injection are much lower than with alternative achalasia therapies, in light of which botulinum toxin tends to be considered specifically in the context of frail patients with severe medical comorbidities [50, 51].

According to multiple smaller studies, DES and jackhammer esophagus also demonstrate a positive response to botulinum toxin injection proximal to the LES. A 2015 study by Marjoux et al. showed that, of six patients with a manometric diagnosis of DES, all had symptomatic improvement at 2 months, and four patients had continued response at 6 months; similarly, of seven patients with jackhammer esophagus, six had symptomatic improvement at 2 months, and five had continued response at 6 months [52]. In a separate prospective, randomized crossover trial of 22 patients with either DES or nutcracker esophagus, 50% short-term (1 month) response in overall symptoms was noted with botulinum toxin injection versus 10% with saline injection [53].

Heller myotomy, a surgical incision of the circular muscle of the LES, often performed with a concomitant antireflux operation, has become a standard tool in the management of achalasia but is less well entrenched in the context of other spastic esophageal disorders. Longer incisions tend to be employed for DES than for classic achalasia. The use of surgical myotomy for patients with DES has been reported with intermittent success in a few decades-old case series, though interpretability is limited by small data sets, case heterogeneity, and variations in technique [54–57]. A prospective study from 2007 showed that extended myotomy with anterior fundoplication had good functional success rates in patients with severe DES, and out of 20 patients, chest pain and dysphagia scores improved in 90 and 100%, respectively [54]. Little data is available regarding the role of surgical myotomy for jackhammer esophagus.

Relative to Heller myotomy, peroral endoscopic myotomy (POEM) has become an alternative and less invasive means of disrupting the LES and may hold more promise in the treatment of the spastic esophageal disorders. POEM utilizes a submucosal tunnel to access the circular muscle fibers, facilitating an adjustment of the final myotomy's length as appropriate to the clinical scenario [58]. While the availability of POEM is expanding, it remains a complex procedure relegated to specialized centers and practitioners [59].

The rates of improvement with POEM in type III achalasia are substantial and comparable over long-term follow-up with other achalasia treatment modalities and with other achalasia subtypes [60]. Several recent case series have also demonstrated successful treatment outcomes with POEM applied in the context of non-achalasia spastic disorders, particularly via the use of a long myotomy including the LES [58, 61–66]. A recent systematic review and meta-analysis aggregated data from 8 observational studies that included a total of 116 patients with type III achalasia, 18 patients with DES, and 37 patients with jackhammer esophagus undergoing POEM, with aggregate success rates of 92, 88, and 72% respectively [67•]. Certain practitioners have advised extra caution when performing POEM in the setting of DES given the technical challenge posed by active contractions, though the systematic review found no difference in adverse event rates with POEM performed among the various spastic disorders [68].

Important caveats to these early reports, however, include the persistently small sample size of cases reported and the lack of randomized trial data. Techniques vary by institution, and as yet there is no consensus on the best method for determining the appropriate length of a myotomy in these circumstances or for selecting individual cases as more appropriate for medical or endoscopic management. Lastly, with attention to background physiology, it seems worth remembering that myotomy is a mechanistically blunt maneuver, agnostic to the means by which a process of hypercontractility or spasm originates or persists.

Conclusion

The spastic esophageal disorders, including jackhammer esophagus, distal esophageal spasm, and type III achalasia, have evolved over time in terms of their manometric definitions. Time-tested diagnostic methods including endoscopy and barium esophagram have been supplemented in recent years with more nuanced HRM parameters and adjunctive technologies like impedance planimetry. Treatment options are also expanding, with older pharmacologic agents being supplemented with newer mechanical techniques, most significantly POEM, though this maneuver's optimal role in the treatment of spastic esophageal disorders has yet to be clarified. Frequent overlaps in nomenclature and management persist alongside important distinctions in pathophysiology. As such, while the diagnostic grouping of the spastic esophageal disorders remains clinically expedient, further research may clarify the extent to which they represent analogous or discrete entities.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major Importance

1.•• Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJPM, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160–74. **The latest iteration of the Chicago Classification represents the current standard for defining esophageal motility disorders, including the spastic esophageal disorders. Relevant updates include the elimination of nutcracker esophagus as a manometric category and the addition of lower esophageal contractility in the calculation of overall hypercontractility.**
2. Roman S, Gyawali CP, Xiao Y, Pandolfino JE, Kahrilas PJ. The Chicago classification of motility disorders: an update. Gastrointest Endosc Clin N Am. 2014;24(4):545–61.
3. Roman S, Pandolfino JE, Chen J, Boris L, Luger D, Kahrilas PJ. Phenotypes and clinical context of hypercontractility in high-resolution esophageal pressure topography (EPT). Am J Gastroenterol. 2012;107(1):37–45.
4. Bredenoord AJ, Fox M, Kahrilas PJ, Pandolfino JE, Schwizer W, Smout AJPM. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil. 2012;24(SUPPL. 1):57–65.
5. Kahrilas PJ, Ghosh SK, Pandolfino JE. Esophageal motility disorders in terms of pressure topography: the Chicago classification. J Clin Gastroenterol. 2008;42:627–35.
6. Behar J, Biancani P. Pathogenesis of simultaneous esophageal contractions in patients with motility disorders. Gastroenterology. 1993;105(1):111–8.
7. Korsapati H, Babaei A, Bhargava V, Mittal RK. Cholinergic stimulation induces asynchrony between the circular and longitudinal muscle contraction during esophageal peristalsis. Am J Physiol Gastrointest Liver Physiol. 2008;294(3):G694–8.
8. Korsapati H, Bhargava V, Mittal RK. Reversal of asynchrony between circular and longitudinal muscle contraction in nutcracker esophagus by atropine. Gastroenterology. 2008;135(3):796–802.
9. Mittal RK, Ren J, McCallum RW, Shaffer HA, Sluss J. Modulation of feline esophageal contractions by bolus volume and outflow obstruction. Am J Phys. 1990;258(2 Pt 1):G208–15.
10. Gyawali CP, Kushnir VM. High-resolution manometric characteristics help differentiate types of distal esophageal obstruction in patients with peristalsis. Neurogastroenterol Motil. 2011;23(6).
11. Börjesson M, Pilhall M, Rolny P, Mannheimer C. Gastroesophageal acid reflux in patients with nutcracker esophagus. Scand J Gastroenterol. 2001;36(9):916–20.
12. Mallet AL, Ropert A, Bouguen G, Siproudhis L, Boutroux D, Bretagne JF, et al. Prevalence and characteristics of acid gastro-oesophageal reflux disease in Jackhammer oesophagus. Dig Liver Dis. 2016;48(10):1136–41.
13. Fang J, Bjorkman D. Nutcracker esophagus: GERD or an esophageal motility disorder. Am J Gastroenterol. 2002;97(6):1556–7.
14. Weiss AH, Iorio N, Schey R. Esophageal motility in eosinophilic esophagitis. Rev Gastroenterol Mex. 2015;80(3):205–13.
15. Martín Martín L, Santander C, Lopez Martín MC, Espinoza-Ríos J, Chavarría-Herbozo C, Gisbert JP, et al. Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. J Gastroenterol Hepatol. 2011;26(9):1447–50.
16. Mandaliya R, DiMarino AJ, Cohen S. Association of achalasia and eosinophilic esophagitis. Indian J Gastroenterol. 2013;32(1):54–7.
17. Konturek T, Lembo A. Spasm, nutcracker, and IEM: real or manometry findings? J Clin Gastroenterol. 2008;42:647–51.
18. Kristo I et. al. Dysphagia severity is related to the amplitude of distal contractile integral in patients with Jackhammer esophagus. Neurogastroenterol Motil. 2017.
19. Khan MQ, AlQaraawi A, Al-Sohaibani F, Al-Kahtani K, Al-Ashgar HI. Clinical, endoscopic, and radiologic features of three subtypes of achalasia, classified using high-resolution manometry. Saudi J Gastroenterol. 2015;21(3):152–7.
20. Almansa C, Heckman MG, Devault KR, Bouras E, Achem SR. Esophageal spasm: demographic, clinical, radiographic, and manometric features in 108 patients. Dis Esophagus. 2012;25(3):214–21.
21. Finnerty BM, Aronova A, Afaneh C, Turkmany KS, Ciecierega T, Crawford CV, et al. Esophageal dysmotility and the utility of barium swallow: an opaque diagnosis. Gastroenterology. 2015;148(4 SUPPL. 1):S1131–2.
22. Matsuura H. Diffuse esophageal spasm: corkscrew esophagus. Am J Med. 2017.
23. Fonseca EK, Yamauchi FI, Tridente CF, Baroni RH. Corkscrew esophagus. Abdom Radiol. 2017;42(3):985–6.
24. Gupta P, Debi U, Sinha SK, Prasad KK. Primary versus secondary achalasia: new signs on barium esophagogram. Indian J Radiol Imaging. 2015;25(3):288–95.
25. Halland M, Ravi K, Barlow J, Arora A. Correlation between the radiological observation of isolated tertiary waves on an esophagram and findings on high-resolution esophageal manometry. Dis Esophagus. 2016;29(1):22–6.
26. Tedesco P, Fisichella PM, Way LW, Patti MG. Cause and treatment of epiphrenic diverticula. Am J Surg. 2005;190(6):891–4.
27. Minami H, Isomoto H, Miuma S, Kobayashi Y, Yamaguchi N, Urabe S, et al. New endoscopic indicator of esophageal achalasia: "pinstripe pattern". PLoS One. 2015;10(2):e0101833.
28. Xiao Y, Carlson DA, Lin Z, Rinella N, Sifrim D, Pandolfino JE. Assessing the pre- and postpeak phases in a swallow using esophageal pressure topography. Neurogastroenterol Motil. 2017;29(9):e13099.
29.• Xiao Y, Carlson DA, Lin Z, Alhalel N, Pandolfino JE. Jackhammer esophagus: assessing the balance between prepeak and postpeak contractile integral. Neurogastroenterol Motil. 2017; https://doi.org/10.1111/nmo.13262. **Utilizing novel interpretations of the distal contractile interval, this recent study of 32 patients with Jackhammer esophagus found that the ratio of post-peak to pre-peak contractile intervals correlated with symptom severity.**
30. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006;290(5):G1033–40.
31. Xiao Y, Kahrilas PJ, Nicodème F, Lin Z, Roman S, Pandolfino JE. Lack of correlation between HRM metrics and symptoms during the manometric protocol. Am J Gastroenterol. 2014;109(4):521–6.
32. Agrawal A, Hila A, Tutuian R, Mainie I, Castell DO. Clinical relevance of the nutcracker esophagus: suggested revision of criteria for diagnosis. J Clin Gastroenterol. 2006;40(6):504–9.
33. Ahuja NK, Clarke JO. The role of impedance planimetry in the evaluation of esophageal disorders. Curr Gastroenterol Rep. 2017;19(2):7.
34.• Carlson DA, Kahrilas PJ, Lin Z, Hirano I, Gonsalves N, Listernick Z, et al. Evaluation of esophageal motility utilizing the functional lumen imaging probe. Am J Gastroenterol. 2016;111(12):1726–35. **This study of 145 patients with non-obstructive dysphagia found that a novel method of evaluating esophageal contractility patterns with an impedance planimetry probe provided additive information regarding pathophysiology not identified by high-resolution manometry alone.**

35. Carlson DA, Lin Z, Kahrilas PJ, et al. The functional lumen imaging probe detects esophageal contractility not observed with manometry in patients with achalasia. Gastroenterology. 2015;149(7): 1742–51.
36. Aspirot A, Faure C. Esophageal dysmotility: characterization and pathophysiology. Dis Esophagus. 2013;26(4):405–9.
37. Patel A, Gyawali CP. How to optimally apply impedance in the evaluation of esophageal dysmotility. Curr Gastroenterol Rep. 2016;18(11).
38. Cho YK. How to interpret esophageal impedance pH monitoring. J Neurogastroenterol Motil. 2010;16(3):327–30.
39. Goldberg MF, Levine MS, Torigian DA. Diffuse esophageal spasm: CT findings in seven patients. Am J Roentgenol. 2008;191(3):758–63.
40. Traube M, Hongo M, Magyar L, McCallum RW. Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. JAMA. 1984;252(13):1733–6.
41. Konturek JW, Gillessen A, Domschke W. Diffuse esophageal spasm: a malfunction that involves nitric oxide? Scand J Gastroenterol. 1995;30(11):1041–5.
42. Eherer AJ, Schwetz I, Hammer HF, Petnehazy T, Scheidl SJ, Weber K, et al. Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. Gut. 2002;50(6):758–64.
43. Lee JI, Park H, Kim JH, Lee SI, Conklin JL. The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. Neurogastroenterol Motil. 2003;15(6): 617–23.
44. Fox M, Sweis R, Wong T, Anggiansah A. Sildenafil relieves symptoms and normalizes motility in patients with oesophageal spasm: a report of two cases. Neurogastroenterol Motil. 2007;19(10):798–803.
45. Pimentel M, Bonorris GG, Chow EJ, Lin HC. Peppermint oil improves the manometric findings in diffuse esophageal spasm. J Clin Gastroenterol. 2001;33(1):27–31.
46. Latimer PR. Biofeedback and self-regulation in the treatment of diffuse esophageal spasm: a single-case study. Biofeedback Self Regul. 1981;6(2):181–9.
47. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstätter M, Lin F, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009;249(1):45–57.
48. Wang L, Li Y-M, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci. 2009;54(11):2303–11.
49. Rohof WO, Salvador R, Annese V, Bruley des Varannes S, Chaussade S, Costantini M, et al. Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology. 2013;144(4):718–25.
50. Lynch KL, Pandolfino JE, Howden CW, Kahrilas PJ. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. Am J Gastroenterol. 2012;107(12):1817–25.
51. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Cochrane Database Syst Rev. 2014;12.
52. Marjoux S, Brochard C, Roman S, Gincul R, Pagenault M, Ponchon T, et al. Botulinum toxin injection for hypercontractile or spastic esophageal motility disorders: may high-resolution manometry help to select cases? Dis Esophagus. 2015;28(8):735–41.
53. Vanuytsel T, Bisschops R, Farré R, Pauwels A, Holvoet L, Arts J, et al. Botulinum toxin reduces dysphagia in patients with nonachalasia primary esophageal motility disorders. Clin Gastroenterol Hepatol. 2013;11(9):1115–21.
54. Leconte M, Douard R, Gaudric M, Dumontier I, Chaussade S, Dousset B. Functional results after extended myotomy for diffuse oesophageal spasm. Br J Surg. 2007;94(9):1113–8.
55. Leconte M, Douard R, Gaudric M, et al. Functional results after extended myotomy for diffuse oesophageal spasm. Br J Surg. 2008;95(125).
56. Elus FH. Esophagomyotomy for noncardiac chest pain resulting from diffuse esophageal spasm and related disorders. Am J Med. 1992;92(5 SUPPL. 1):S129–31.
57. Henderson RD, Ryder D, Marryatt G. Extended esophageal myotomy and short total fundoplication hernia repair in diffuse esophageal spasm: five-year review in 34 patients. Ann Thorac Surg. 1987;43(1):25–31.
58. Khashab MA, Messallam AA, Onimaru M, et al. International multicenter experience with peroral endoscopic myotomy for the treatment of spastic esophageal disorders refractory to medical therapy (with video). Gastrointest Endosc. 2015;81(5):1170–7.
59. Von Renteln D, Fuchs KH, Fockens P, et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. Gastroenterology. 2013;145(2).
60. Meng F, Li P, Wang Y, Ji M, Wu Y, Yu L, et al. Peroral endoscopic myotomy compared with pneumatic dilation for newly diagnosed achalasia. Surg Endosc. 2017;31(11):4665–72.
61. Shiwaku H, Inoue H, Beppu R, Nakashima R, Minami H, Shiroshita T, et al. Successful treatment of diffuse esophageal spasm by peroral endoscopic myotomy. Gastrointest Endosc. 2013;77(1):149–50.
62. Louis H, Covas A, Coppens E, Devière J. Distal esophageal spasm treated by peroral endoscopic myotomy. Am J Gastroenterol. 2012;107(12):1926–7.
63. Kandulski A, Fuchs KH, Weigt J, Malfertheiner P. Jackhammer esophagus: high-resolution manometry and therapeutic approach using peroral endoscopic myotomy (POEM). Dis Esophagus. 2016;29(6):695–6.
64. Bechara R, Ikeda H, Inoue H. Peroral endoscopic myotomy for Jackhammer esophagus: to cut or not to cut the lower esophageal sphincter. Endosc Int Open. 2016;4(5):E585–8.
65. Kuwano H, Miyazaki T, Masuda N, Kato H, Kusano M. Long myotomy of the esophagus and gastric cardia with a complete fundic patch procedure for diffuse esophageal spasm. Hepato-Gastroenterology. 2004;51(60):1729–31.
66. Youn YH, Minami H, Wai P, Chiu Y, Park H. Peroral endoscopic myotomy for treating achalasia and esophageal motility disorders. J Neurogastroenterol Motil. 2016;22(1):2093–879.
67.• Khan MA, Kumbhari V, Ngamruengphong S, Ismail A, Chen YI, Chavez YH, et al. Is POEM the answer for management of spastic esophageal disorders? A systematic review and meta-analysis. Dig Dis Sci. 2017;62(1):35–44. **This systematic review and meta-analysis of 8 trials comprising 179 patients with spastic esophageal disorders concluded that peroral endoscopic myotomy was a safe and effective treatment option for all three diagnoses. An important caveat is that patients with Type III achalasia ($n = 116$) significantly outnumbered patients with jackhammer esophagus ($n = 37$) and distal esophageal spasm ($n = 18$).**
68. Ponds FAM, Smout AJPM, Fockens P, Bredenoord AJ. Challenges of peroral endoscopic myotomy in the treatment of distal esophageal spasm. Scand J Gastroenterol. 2018:1–4.