# Hypercontractile Esophagus From Pathophysiology to Management: Proceedings of the Pisa Symposium

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**Hypercontractile esophagus (HE) is a heterogeneous major motility disorder diagnosed when ≥20% hypercontractile peristaltic sequences (distal contractile integral >8,000 mm Hg*s*cm) are present within the context of normal lower esophageal sphincter (LES) relaxation (integrated relaxation pressure < upper limit of normal) on esophageal high-resolution manometry (HRM). HE can manifest with dysphagia and chest pain, with unclear mechanisms of symptom generation. The pathophysiology of HE may entail an excessive cholinergic drive with temporal asynchrony of circular and longitudinal muscle contractions; provocative testing during HRM has also demonstrated abnormal inhibition. Hypercontractility can be limited to the esophageal body or can include the LES; rarely, the process is limited to the LES. Hypercontractility can sometimes be associated with esophagogastric junction (EGJ) outflow obstruction and increased muscle thickness. Provocative tests during HRM can increase detection of HE, reproduce symptoms, and predict delayed esophageal emptying. Regarding therapy, an empiric trial of a proton pump inhibitor, should be first considered, given the overlap with gastroesophageal reflux disease. Calcium channel blockers, nitrates, and phosphodiesterase inhibitors have been used to reduce contraction vigor but with suboptimal symptomatic response. Endoscopic treatment with botulinum toxin injection or pneumatic dilation is associated with variable response. Per-oral endoscopic myotomy may be superior to laparoscopic Heller myotomy in relieving dysphagia, but available data are scant. The presence of EGJ outflow obstruction in HE discriminates a subset of patients who may benefit from endoscopic treatment targeting the EGJ.**

*Am J Gastroenterol 2021;116:263–273. https://doi.org/10.14309/ajg.0000000000001061*

## INTRODUCTION

High-resolution manometry (HRM) was first introduced in the evaluation of esophageal motor function using water perfused manometry catheters in the 1990s, which transitioned to the use of solid-state circumferential pressure sensors and digital data capture in the next decade (1–3).

Early HRM studies defined 3 contraction segments in the esophageal body, the proximal skeletal muscle contraction segment, and 2 distal smooth muscle contraction segments (1).

Exaggerated esophageal body contraction, termed "nutcracker esophagus" based on mean distal esophageal contraction amplitudes >180 mm Hg, was described previously with standard manometry (4) and with initial HRM reports as merging together of the 2 smooth muscle contraction segments (2).

The Chicago Classification (Figure 1) uses 3 software tools, the integrated relaxation pressure (IRP), distal latency (DL), and distal contractile integral (DCI) to characterize lower esophageal sphincter (LES) and esophageal body motor function. Using these tools, hypercontractile esophagus (HE) describes higher esophageal body contraction vigor than that observed in healthy individuals (5). This review focuses on the current understanding of HE and highlights recent research that provides further insight into the pathophysiology, diagnosis, and management of this disorder.

## DEFINITION OF HE

A hypercontractile swallow is diagnosed when DCI exceeds 8,000 mm Hg*s*cm. A diagnosis of HE requires at least 20% hypercontractile swallows on a supine 10 swallow HRM protocol (5). Esophageal hypercontractility can either be limited to the esophageal body, or the hypercontractile process can include the LES. Rarely, the process is limited to the LES (6). However, extending the DCI measurement box to include the LES does not seem to increase the yield of HE diagnosis (7).

The manometric pressure profile of esophageal peristalsis can be further broken down into prepeak and postpeak phases before and after the point of highest contraction amplitude (Figure 2).When

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**Received May 7, 2020; accepted October 22, 2020; published online December 3, 2020**

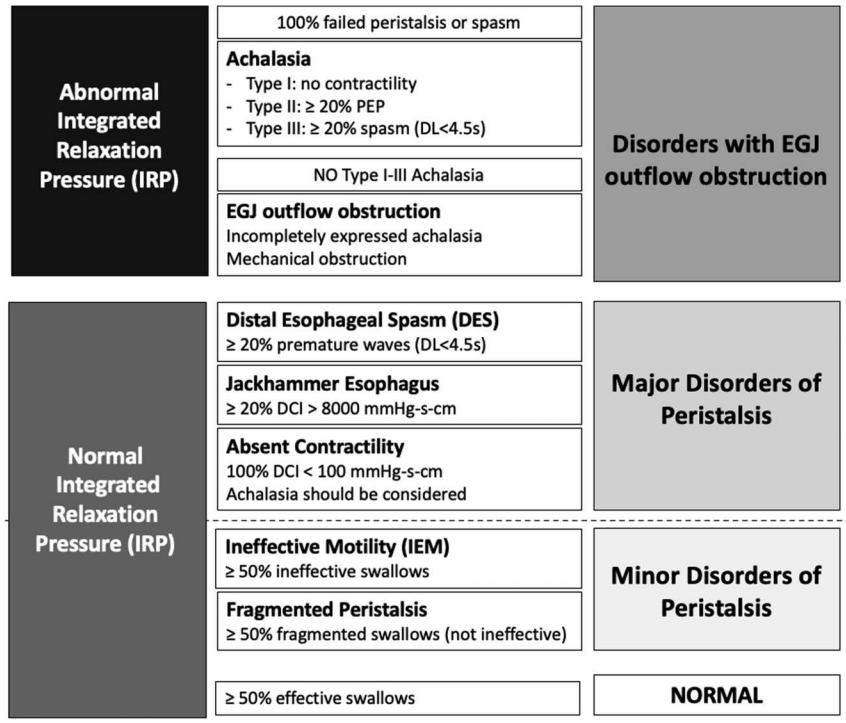


**Figure 1.** The Chicago Classification V3.0. DCI, distal contractile integral; DES, distal esophageal spasm; DL, distal latency; EGJ, esophagogastric junction; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; PEP, panesophageal pressurization.

hypercontractility was categorized into prepeak vs postpeak hypercontractility, the postpeak hypercontractility variant was associated with higher overall contraction vigor (8). Other studies have linked higher contraction vigor to more symptoms (both dysphagia and chest pain) (9–11). The pattern of hypercontractility has also been studied, with some hypercontractile peristalsis demonstrating multiple peaks of contraction in synchrony with respiration (12). The term "jackhammer esophagus" is applied to a subset of HE disorders where chaotic and repetitive esophageal contraction is noted in motor patters fulfilling HE criteria. Finally, a new significant element in HE definition is the association with esophagogastric junction outflow obstruction (EGJOO).

## PATHOPHYSIOLOGY OF EXAGGERATED ESOPHAGEAL CONTRACTION

A volitional swallow initiates a coordinated contraction of the circular and longitudinal smooth muscle of the esophagus (primary peristalsis). Secondary peristalsis is induced by esophageal distention. Activation of inhibitory nerves occurs simultaneously in the entire esophagus immediately after swallowing (deglutitive inhibition), followed by peristaltic contraction from activation of excitatory neurons (13,14). In addition, longitudinal muscle contraction can stretch and activate mechanosensitive inhibitory motor neurons to cause nitric oxide–mediated inhibition in distal esophagus (15). Bolus information can modify esophageal peristalsis through intramural neuromuscular reflexes and can affect the strength and speed of esophageal peristalsis (16–19).

Hypercontractility is a primary motor disorder of the esophageal body where an excess of excitatory cholinergic drive, associated with temporal asynchrony of circular and longitudinal muscle contractions, leads to exaggerated smooth muscle contraction (5,11,20,21). Abnormal peripheric neural control or histopathologic esophageal modification could play a key role. In jackhammer esophagus, the HE subset with prolonged, repetitive, and chaotic postpeak contractions, uncoordinated propagation of the pressure peak may imply an inhibitory defect beyond the latency interval, potentially even peripherally within the myogenic response (8,22). These abnormalities could be related to abnormal muscular calcium sensitivity or some unknown or exaggerated trigger that elicits contraction during the relaxation phase.

There is recent evidence linking HE with EGJOO (23). There are 2 possible pathophysiologic mechanisms for this association. First, HE may be a secondary phenomenon arising from a distal obstructive process. Some patients with abnormal IRP within the realm of EGJOO have a hypercontractile pattern in the esophageal body (20,24), as evidenced by studies using functional lumen imaging probe (FLIP) (11,25), and this is further corroborated by short symptomatic relief with treatment of the obstructive process (26). Second, HE may be caused in part by abnormal esophageal inhibition, which also causes incomplete EGJ relaxation with swallows. When esophageal contraction and inhibition are studied using provocative testing, hypercontractile patients with and without an obstructive EGJ pattern demonstrate similar exaggerated esophageal excitation, with elements of abnormal esophageal inhibitory function (20,27). Experimentally, scavenging nitric oxide with free hemoglobin in control subjects induces simultaneous esophageal contraction and inhibits deglutitive EGJ relaxation (28). Furthermore, several histopathologic changes have been described in spastic esophageal motor disorders that resemble those seen in achalasia, including loss of ganglionic cells in the myenteric plexus (29) and interstitial cells of Cajal (30). Lymphocytic inflammation has been reported in the vicinity of the myenteric

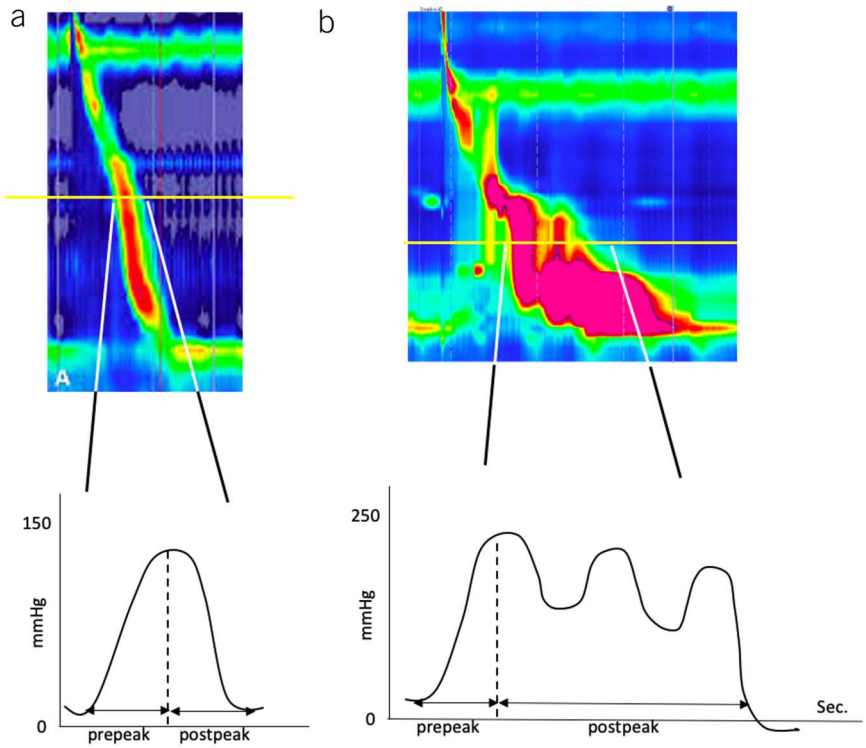


**Figure 2.** Image describing the separation of prepeak phase and postpeak phase in a peristaltic wave. (**a**) Normal swallow with normal balance between prepeak and postpeak phase. (**b**) Jackhammer esophagus, where the presence of repetitive contraction generates an imbalance between the 2 phases with a prolonged postpeak phase.

plexus in spastic disorders (31), similar to achalasia (32). Finally, eosinophilic inflammation and eosinophilic esophagitis (EoE) might be associated with abnormal motor function (24,33–35) and could play a role in the genesis of both HE and achalasia in some instances (Figure 3). Patients with HE and obstruction thus seem to have similar neural dysfunction as those fulfilling the Chicago Classification 3.0 definition of HE. These physiologic and histopathologic findings support the role of abnormal inhibition in HE pathophysiology and demonstrate shared pathophysiology between HE, HE with EGJOO, and achalasia. Increased esophageal smooth muscle thickness has also been reported in spastic disorders, which is likely a secondary phenomenon rather than a cause of these disorders (36–38).

## ETIOLOGY

Although most cases of HE are idiopathic, hypercontractility has been reported to occur in the context of EGJ mechanical obstruction, gastroesophageal reflux disease (GERD), and opiate use. Esophageal hypercontractility has been observed in patients with inflated gastric lap-bands (39). Esophageal acid perfusion in patients with noncardiac chest pain can induce multipeaked, repetitive, spontaneous, or simultaneous esophageal contractions (40). HE has also been associated with GERD in approximately 40% of patients (41,42). Certain medications might be associated with esophageal hypercontractility, of which opiates are gaining notoriety. Opiates can impair LES relaxation, decrease DL, and increase esophageal contractile amplitude (43–45). In chronic opioid users, EGJ outflow obstruction and type III achalasia were more likely to be diagnosed when HRM was performed on-medication than off-medication, while distal esophageal spasm (DES) and HE had similar incidence on- and off-medications (45).

## CLINICAL PRESENTATION

HE is a rare condition that ranges from 1.5% to 3% of manometric diagnoses in advanced motility centers (42,46,47). Increased vigor of peristaltic contractions and HE with or without outflow obstruction on HRM can manifest with dysphagia and chest pain (6,11,20,48). However, these symptoms do not consistently improve after pharmacologic or endoscopic therapies to induce smooth muscle relaxation (49–52), and the exact mechanism of symptom generation remains unclear.

An European cohort study reported two-thirds of patients with HE present with dysphagia, which may associate with degree of hypercontractility and intrabolus pressure (23). Some patients recorded chest pain that did not associate with manometric features (23). Another study of 30 patients with HE observed both dysphagia (53%) and chest pain (40%), but only dysphagia was significantly associated with DCI values (9). In another small series of patients with HE, among those with dysphagia as main symptom, half had incomplete LES relaxation (53). More recently, a larger international series of HE observed that dysphagia was more frequent in patients with HE with EGJOO, while heartburn and chest pain were associated with HE without obstruction (20). Finally, Xiao et al. reported higher dysphagia symptom scores when the hypercontractile pattern, especially the pressure wave peak, propagated in a chaotic fashion in the smooth muscle esophagus (8,22).

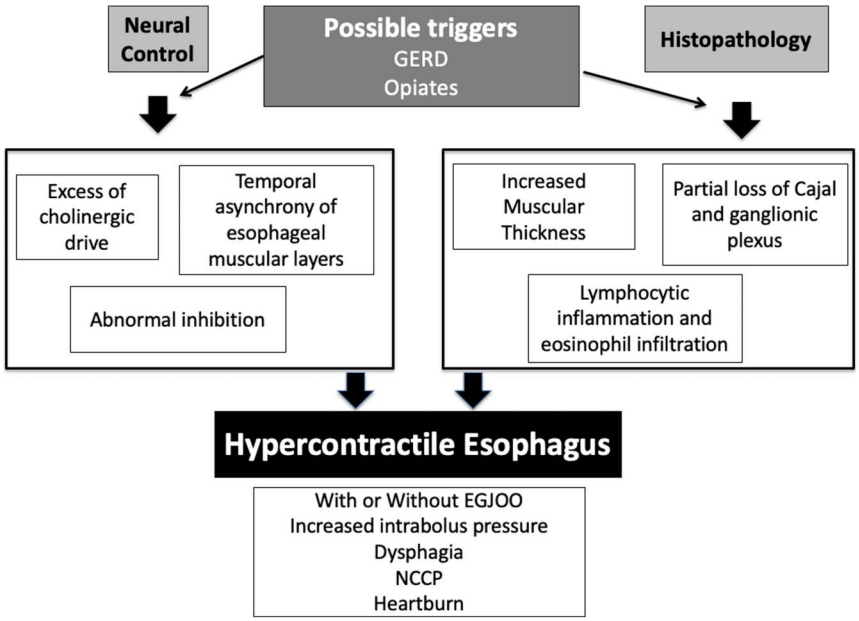


**Figure 3.** Pathophysiology of hypercontractile esophagus. Neural control of esophageal smooth muscle contraction from the brain stem vagal nuclei is modulated by peripheral sensory data. Excess of cholinergic drive as well temporal asynchrony of esophageal mucosal layer. On the other hand, histopathologic changes as loss of plexus ganglionic cells and interstitial cells of Cajal associated to an eosinophil and lymphocytic infiltration play a determinant role in the genesis of HE. GERD, opiates and anticholinergic medication as triggers better define the genesis of HE. GERD, gastroesophageal reflux disease; EGJOO, esophagogastric junction outflow obstruction; NCCP, noncardiac chest pain.

## UPPER ENDOSCOPY AND BARIUM ESOPHAGOGRAPHY

Upper endoscopy with biopsy should be performed for initial evaluation of esophageal transit symptoms to exclude mechanical obstruction, esophageal stenosis, or esophagitis (including EoE). Endoscopic findings are neither sensitive nor specific for motor disorders, although increased resistance to endoscope passage may be encountered in achalasia and spastic disorders.

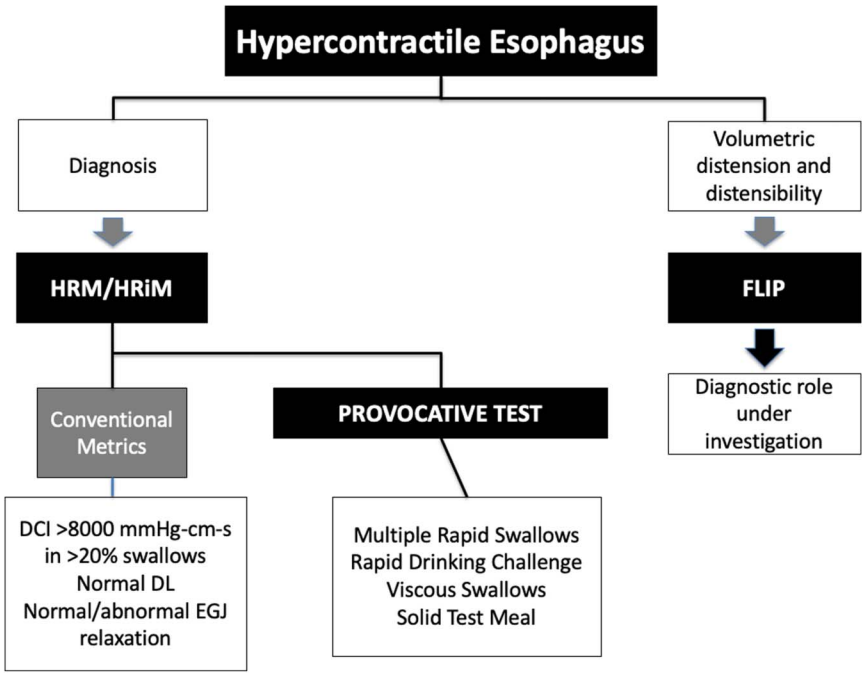


**Figure 4.** Diagnosis of hypercontractile esophagus is based on ≥20% hypercontractile waves (DCI >8,000 mm Hg*s*cm) during high-resolution manometry (HRM) or high-resolution impedance manometry (HRiM) with or without normal EGJ relaxation. Supplementary evaluation can be personalized based on the clinical scenario being evaluated, using provocative tests. Esophageal functional lumen imaging probe (FLIP) assessment maybe helpful for defining the role of EGJ obstruction in determining hypercontractility. DCI, distal contractile integral; DL, distal latency; EGJ, esophagogastric junction

**Table 1. High-resolution manometry characteristics in the evaluation of hypercontractile motility disorders**

| | HRM characteristics | Comments |
|---|---|---|
| Single swallow (SS) | | |
| Effective hypercontractile | DCI 450–8,000 mm Hg*s*cm; DCI >8,000 mm Hg*s*cm | IRP < upper limit of normal; IRP < upper limit of normal or IRP > upper limit of normal (EGJOO and HE may overlap) |
| Provocative tests | | |
| Multiple rapid swallow (MRS) (65,72) | Incomplete esophageal body inhibition and exaggerated excitation with absence of contraction reserve compared with SS (20) | MRS-DCI/SS-DCI < 1 with/without abnormal LES function |
| Rapid drinking challenge (RDC) (65) | Brief hyperpressurized pattern (67); Some degree of EGJ obstruction (68); IRP >17 mm Hg is predictor of obstruction (105); Esophageal shortening and panesophageal pressurization (69) | There is not a consensus regarding the finding observed during RDC |
| Viscous or solid swallow | Poor correlation among symptoms and HRM findings | The value of viscous/solid swallows is limited, and no data exist directly pertaining to HE |
| Solid test meal (STM) (75) | STM unmask major motility disorders (80% included HE or DES) | Larger number of patients reported their usual symptom during the STM in contrast to SS |
| Diagnosis (5) | | |
| HE | ≥20% hypercontractile waves | IRP < upper limit of normal |
| Proposed HE criteria | | |
| Traditional HE | ≥20% hypercontractile waves, with abnormal inhibition during MRS; ≥20% hypercontractile waves; multiple or chaotic peak (jackhammer esophagus) | DL and IRP < upper limit of normal |
| HE with obstruction | ≥20% hypercontractile waves involving body and LES with EGJ obstruction | IRP > upper limit of normal |

DCI, distal contractile integral; DES, distal esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; HE, hypercontractile esophagus; HRM, high-resolution manometry; IRP, integrated relaxation pressure (upper limit of normal varies with HRM manufacturer); LES, lower esophageal sphincter.

Barium esophagography provides information on esophageal anatomy that is complementary to endoscopy (54). The decision regarding which test to order first depends in large part on which is most likely to yield the diagnosis. Endoscopy is commonly the first test used to evaluate solid food dysphagia or food impaction because it allows for precise mucosal inspection and the ability to biopsy to rule out EoE (55,56). On the other hand, barium esophagography provides greater information on motility disorders and is superior to endoscopy in this regard (57,58). Barium radiology will identify structural abnormalities such as diverticula, strictures, rings, webs, and tumors. It can demonstrate a corkscrew pattern in DES, and abnormal esophageal emptying with EGJ outflow obstruction, but findings specific for HE have not been described.

## MANOMETRIC FEATURES

According to Chicago Classification 3.0 metrics, hypercontractile peristalsis requires normal LES relaxation (normal IRP), normal timing of peristalsis (normal DL), and exaggerated smooth muscle peristalsis (abnormal DCI >8,000 mm Hg*s*cm) (12). The presence of 2 or more hypercontractile sequences defines HE using Chicago Classification 3.0 (5).

However, there is much more to this disorder than that described in the simple definition provided by Chicago Classification 3.0 (Figure 4). The hypercontractile pattern can be associated with abnormal EGJ opening (25) and possibly reduced deglutitive inhibition noted during multiple rapid swallows (MRSs) (11). In addition, the contractile pattern morphology can be heterogeneous, with large variation in contractile vigor, differences in prepeak and postpeak DCI and varied patterns of peak propagation (23). Thus, the hypercontractile pattern is much more complex than a simple disorder of hypercontractility, which is further evident from the fact that many patients do not respond to smooth muscle relaxants.

Based on these concepts, we propose that hypercontractile esophageal disorder is an umbrella term that can include the following phenotypes (Table 1):

1. Traditional HE, characterized by exaggerated smooth muscle peristalsis (abnormal DCI >8,000 mm Hg*s*cm), with normal LES relaxation (normal IRP) and normal timing of peristalsis (normal DL), but with evidence of abnormal inhibition during MRS. A considerable proportion of patients with HE demonstrate abnormal inhibition during MRS, which can be associated with an obstructive pattern during rapid drink challenge (RDC), and presentation that includes dysphagia (11,20). This phenotype describes a latent obstructive pattern that is only evident on provocative testing, and not evident on standard HRM. A

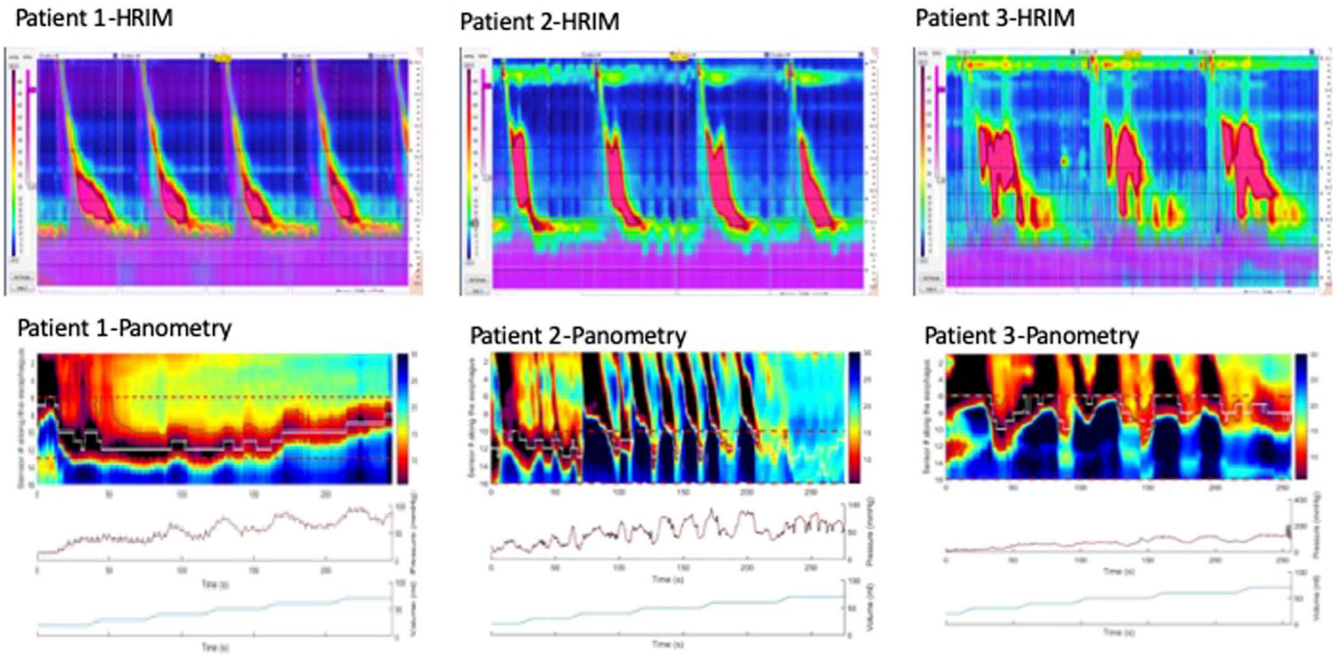


**Figure 5.** Three hypercontractile esophagus patient examples are shown. The top panels are representative examples of the HRIM of the 3 patients. The pressure and impedance ranges are on the left and the spatial length from the pharynx to the stomach is noted on the right. The FLIP panometry of the same 3 patients are shown on the bottom panels below the HRIM study. The top panel of the panometry evaluation is a FLIP topography plot and the color scale for diameter. The blue color represents high diameters, and the red color represents low diameters with the black color supporting complete lumen closure. The red tracing is pressure, and the blue tracing below is the volume distention. Patient 1 represents an example of a jackhammer pattern associated with a normal IRP values, average DCI values of approximately 15,000 mm Hg*s*cm and no overt multiple peaks. This patient seemed to have an achalasia-like pattern with poor EGJ opening on panometry with an EGJ-DI of less than 1.0 and no discernible contractile activity. The pressures during the FLIP distention were high supporting decreased compliance in the esophageal wall that could be reactive or mechanical. Patient 2 also has a jackhammer pattern with a borderline IRP and a hypercontractile pattern associated with some double peaks and an average DCI of approximately 10,000 mm Hg*s*cm. The panometry panel is showing a slow frequency RAC pattern with 3–4 contractions that are completely occluding. Typically, RACs occur at a frequency of 6–8 in normal controls, and the lumen obliteration is much shorter in the space-time domain. There is evidence of normal EGJ opening; however, the sphincter is moving up into the chest with each propagating contraction and the max diameters of the EGJ are normal at higher distention volumes. Patient 3 fulfills CC 3.0 criteria for jackhammer; however, the morphology of the contraction is extremely abnormal. The panometry evaluation suggests that the LES has moved high into the chest and it is associated with a sustained prolonged lumen occluding contraction that is associated with extremely high intrabag pressures over 100 mm Hg. The FLIP does tend to mirror the findings seen on HRIM, and there does seem to be additional important information regarding esophageal function that can be gleaned from the panometry. CC, Chicago Classification; DCI, distal contractile integral; DI, distensibility index; DL, distal latency; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; HRIM, high-resolution manometry and impedance; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; RAC, repetitive antegrade contraction.



further subtype of traditional HE is Jackhammer esophagus, a subset of HE characterized by exaggerated smooth muscle peristalsis (DCI >8,000 mm Hg*s*cm) with multiple or chaotic peaks, with normal LES relaxation (normal IRP), and normal timing of peristalsis (normal DL).

2. HE with obstruction, characterized by exaggerated smooth muscle peristalsis (abnormal DCI >8,000 mm Hg*s*cm) involving both LES and esophageal body, and EGJ obstruction defined on the basis of elevated IRP. This phenotype may potentially arise from high degree of abnormal inhibition that determines an abnormal LES (EGJ) relaxation (20), abnormal esophageal wall compliance (59), or distal mechanical obstruction with compensatory increase in esophageal body contraction (60,61).

Future prospective cohort studies, including physiological or pharmacologic provocative testing during HRM as well as FLIP, will be useful in further understanding the underlying pathophysiology of these phenotypes.

## PROVOCATIVE TESTING DURING HRM

The rationale for use of provocative testing during HRM lies in the fact that in everyday life symptoms generally occur during swallowing of solids and/or while rapidly drinking liquids. Two provocative tests, RDC and MRSs, have been recommended for inclusion in routine HRM protocols (62–64).

### Rapid drink challenge

RDC consists of rapidly drinking 100–200 mL of water in the upright position. In healthy subjects, rapid drinking induces complete inhibition of esophageal body contraction (hypopressive pattern) and relaxation of the LES; in 50%–70%, a peristaltic wave follows (65,66). In patients with HE, a brief hyperpressurized pattern has been observed, in contrast to a prolonged hyperpressurized pattern in achalasia (67). Presence of one of the following: >2 pressurizations at >20 mm Hg, >8% of time above 20 mm Hg, or a EGJ gradient of >4 mm Hg discriminated the hyperpressurized pattern with a sensitivity of

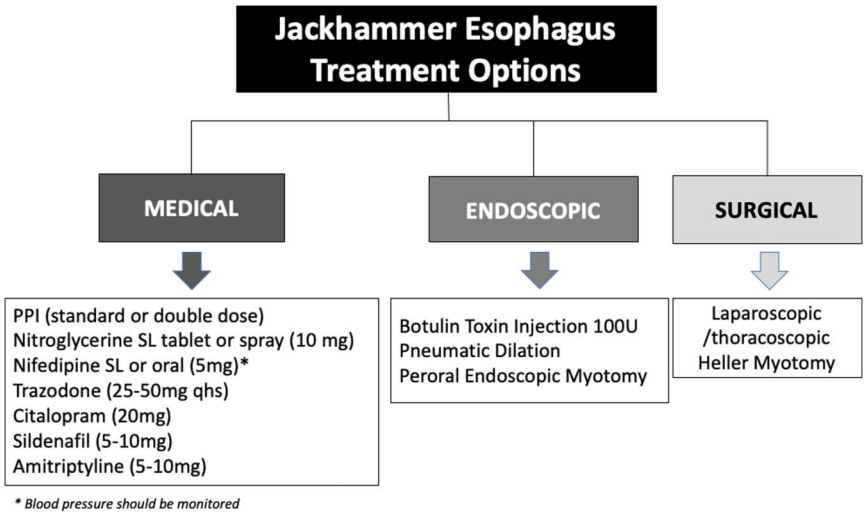


**Figure 6.** Management of hypercontractile esophagus. PPI, proton pump inhibitors; SL, sublingual.

80% and a specificity of 93% (67). Others have looked at specific patterns during RDC, including esophageal shortening and panesophageal pressurization, which predicted more severe dysphagia in EGJOO (68,69), and were seen in half of patients with HE (70). Early panesophageal pressurization with provocative testing has been reported in disorders of abnormal esophageal compliance, including EoE, and could result from thickened esophageal muscle in HE.

### Multiple rapid swallows

MRS consists of 5 swallows of 2 mL of water at 2- to 3-second intervals, repeated 3 times for improving accuracy (71), seems useful in investigating inhibitory and excitatory neural pathways. In the 2 published series of healthy subjects, MRS induced complete inhibition in 76%–95% and augmentation of contractile vigor after MRS compared with single water swallows, termed contraction reserve, in 80% (65,72). A recent multicenter study demonstrated HE, HE with obstruction, and achalasia type III have a common pathophysiological thread combining incomplete inhibition and exaggerated excitation with absence of contraction reserve in many patients regardless of the presence or absence of abnormal LES function (20).

### Viscous/solid swallows

Use of viscous/solid swallows may induce typical symptoms in one-third of the patients during HRM studies, although without correlation between HRM metrics during swallows and symptoms (73), and with overall very low yield in identifying major motor disorders (74).

### Solid test meal

Ang et al. (75) have shown that a consistent number of patients with dysphagia and minor motility disorders or normal manometry diagnosed using single water swallows were diagnosed as EGJOO, HE, or DES using solid test meal. Furthermore, 63% of patients reported their usual symptom during solid test meal in contrast to 1% during SWS, more often with major motility disorders (around 80% of the patients including HE and DES).

In summary, provocative tests have shown potential to increase detection of HE, reproduce symptoms, predict delayed esophageal emptying, and aid in understanding of pathophysiology.

## DISTENSIBILITY USING FLIP

FLIP assesses both EGJ opening dynamics and the contractile response to sustained volumetric distention and has evolved over the past 5 years (76). Using FLIP, measurement of lumen diameter across a space time domain along the distal esophagus and through the EGJ (77) was leveraged into a new analysis paradigm called panometry (59). Although data are limited and primarily descriptive, novel response patterns have been observed in patients with HE who may help explain the range of symptom presentations and the varying prognosis (78). Although some patients with HE may have a relatively normal FLIP with repetitive antegrade contractions, others have a very abnormal pattern associated with excessive LES lift and sustained occluding contractions that extend along the entire length of the distal esophagus (Figure 5); yet, others may have absent contractility. In addition, there may be evidence of EGJOO in many of these patients despite a normal IRP on HRM. Whether obstruction is the cause of the hypercontractile pattern or a component of the motility abnormality that is driving hypercontractility remains unclear. Evidence from elegant physiologic and morphologic studies from Mittal et al. demonstrates that obstruction can cause a reactive hypercontractile pattern (61).

Currently, it is premature to predict how panometry will help explain the varying patterns and presentations of HE. Future research will require a multicenter approach assessing outcome and prognosis as this entity is rare.

## MEDICAL MANAGEMENT

Medical treatment is the first-line treatment approach to patients with HE. The primary goal of treatment is control of the most common symptoms (dysphagia and chest pain); an additional goal is reduction of vigor of the abnormal esophageal contractions (79).

GERD, psychiatric comorbidity, and esophageal visceral hypersensitivity have been suggested as potential mechanisms for symptoms. In patients presenting with chest pain, an empirical

**Table 2. Gaps in current understanding of hypercontractile esophageal disorder**

| Gaps in current understanding | Future directions |
|---|---|
| Etiology of HE | Longitudinal follow-up studies in patients with and without eosinophilic infiltration to better understand the prevalence and the role of eosinophils in HE |
| Heterogeneity within HE | Longitudinal follow-up studies in patients with and without EGJ obstruction |
| Diagnostic criteria for clinically relevant HE | EGJ obstruction should be considered in patients with HE |
| Role of provocative testing | Prospective studies to better define the role of RDC and STM; prospective studies to evaluate the role of MRS in predicting the outcome of HE with and without obstruction |
| Role of novel esophageal physiologic tests | Prospective studies by means of FLIP to evaluate whether obstruction is the cause of the hypercontractile pattern or a component of the motility abnormality that drives HE |
| Impact on patient presentations and symptoms | Cross-sectional studies to assess the natural history of this motor disorder |
| Role of therapy | Prospective and RCTs to evaluate the effects on HRM finding and symptoms of both medical treatments (TCAs, SSRI, and 5-phosphodiesterase) and POEM |
| Long-term impact of a diagnosis of HE | Longitudinal studies evaluating outcome, complications, and impact on quality of life |

EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; HE, hypercontractile esophagus; HRM, high-resolution manometry; MRS, multiple rapid swallow; POEM, per-oral endoscopic myotomy; RCT, randomized controlled trial; RDC, rapid drinking challenge; SSRI, selective serotonin reuptake inhibitors; STM, solid test meal; TCA, tricyclic acid.

PPI trial can be first considered (41,49). As many as 43% of patients with HE may have GERD-related symptoms, and treatment with PPIs has potential to improve not just chest pain, but also dysphagia (41). There are reports of hypercontractility in patients with EoE, where treatments that reduce eosinophilic counts may also resolve hypercontractility, suggesting abnormal wall compliance or stenosis drives hypercontractility in these patients. This is another reason to consider PPI therapy, or alternatively, topical steroids (80). Among pain modulators, only trazodone has shown superiority over placebo in treating patients with DES or hypertensive peristalsis (nutcracker esophagus) (81). Selective serotonin reuptake inhibitors (sertraline, paroxetine, venlafaxine, and citalopram) and tricyclic antidepressants have efficacy in controlling perceptive esophageal symptoms (82–84).

There is limited evidence that the asynchrony between circular and longitudinal esophageal smooth muscle contraction in HE could be corrected by blocking cholinergic neurotransmission using atropine (85). Calcium channel blockers, nitrates, and phosphodiesterase inhibitors have also been used to reduce contraction vigor. Calcium channel antagonists inhibit intracellular calcium uptake, with potential to reduce esophageal contraction vigor and lower LES pressures (86). In studies of DES patients with small sample sizes, observed chest pain improvement may have been from placebo effect rather than a direct medication effect (51,87). Phosphodiesterase-5 inhibitors block the degradation of nitric oxide resulting in a more prolonged esophageal smooth muscle relaxation. Although contractile amplitude and propagation velocity are both reduced in healthy volunteers and in patients with motility disorders, this does not consistently translate into symptom improvement (88,89).

## ENDOSCOPIC AND SURGICAL MANAGEMENT

The relief of dysphagia and chest-pain represent the goal of endoscopic treatments for HE. Other studies evaluating these endoscopic therapies demonstrated variable results, with sustained symptom relief ranging from 12% to 100% (90–92), and with spastic features on HRM a possible predictor of poor outcome (93). In small series, botulinum toxin injection showed symptomatic improvement lasting up to 6–12 months (52,94). A larger series of patients showed 22%–50% of symptomatic response to invasive endoscopic treatments (pneumatic dilation and botulinum toxin injection) (6,95).

Because HE is characterized by distal esophageal body hypercontractility, sometimes in conjunction with abnormal LES relaxation, myotomy has been proposed as a potential management option. Both per-oral endoscopic myotomy (POEM) and laparoscopic Heller myotomy have been studied with variable results, but available data are scant (96).

POEM has potential to nullify the hypercontractile segment of smooth muscle esophagus, and potentially help symptoms. In open-label experience of POEM in spastic esophageal disorders, symptomatic benefit has been reported in as many as 93% (70% in HE) with a mean myotomy length of 16 cm and with <10% complications (97,98). Other anecdotal reports similarly suggest benefit, especially if the LES is included in the myotomy (99–101).

Treating HE with conventional laparoscopic Heller myotomy, which usually extends only 5 cm to the esophagus and 2 cm to the stomach, may not be as effective as POEM. Specific outcomes in HE are scant. All treatment options are summarized in Figure 6.

## PROGNOSIS

There are very limited data on the natural history of HE. A retrospective study showed that 25% of 12 patients with HE progressed to type III achalasia over a mean of 24 months, and impaired EGJ relaxation was the only risk factor that predicted progression to achalasia (102). In another retrospective study assessing patients with HE, in the presence of spastic hypercontractility (with short DL), 33.3% were unresponsive to both anticholinergic drugs and phosphodiesterase-5 inhibitors (103). Furthermore, recent data from a randomized trial evaluating the efficacy of botulinum toxin injection in symptomatic hypercontractile esophageal disorders (HE, DES, and type 3 achalasia) reported significant symptom improvement with both active treatment and sham arms (104). Finally, a retrospective study with phone survey using the impact dysphagia questionnaire found that only a minority of patients with EGJOO and HE reported symptoms, and symptom persistence was predicted by the maximal DCI and IRP values in both groups (24). However,

many research gaps remain and require further investigation (Table 2).

Most patients with HE have a benign clinical course similar to controls despite the absence of specific treatment. However, the combination of abnormal IRP and high DCI seems to discriminate an important subset of patients with HE who may benefit from invasive management. Therefore, the HE phenotypes proposed may have clinical relevance, but needs further study. Finally, FLIP panometry could be helpful in this setting in further stratifying patients requiring treatment vs simple follow-up.

## CONFLICTS OF INTEREST

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**Financial support:** None to report.

**Potential competing interests:** N. de Bortoli: no disclosures. P. C. Gyawali: consulting: Medtronic, Diversatek, Isothrive, Ironwood, and Quintiles. S. Roman: consulting Medtronic and research support Diversatek Healthcare and Medtronic. S. Tolone: no disclosures. D. Sifrim: research grants: Reckitt Benckiser UK, Jinshan Technology China, and Alfa Sigma Italy. R. Tutuian and R. Penagini: no disclosures. J. E. Pandolfino: Medtronic, Diversatek, Torax, Ironwood, Takeda, and AstraZeneca (consulting); Impleo (research funding); and Crospon (stock options). E. V. Savarino: lecture fee: Medtronic, Takeda, Janssen, MSD, AbbVie, and Malesci; consulting: Medtronic, Takeda, Janssen, MSD, Reckitt Bencikser, Sofar, Unifarco, SILA, and Oftagest.

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