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MINI REVIEW

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The hypercontractile esophagus: Still a tough nut to crack

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Abstract

Hypercontractile esophagus (HE), also known as jackhammer esophagus, is an esophageal motility disorder. Nowadays, high-resolution manometry (HRM) is used to diagnose the disorder. According to the latest iteration of the Chicago classification, HE is present when at least 2 out 10 liquid swallow-induced peristaltic waves have an abnormally high Distal Contractile Integral. In the era of conventional manometry, a similar condition, referred to as nutcracker esophagus, was diagnosed when the peristaltic contractions had an abnormally high mean amplitude. Although the HRM diagnosis of HE is relatively straight-forward, effective management of the disorder is challenging as the correlation with symptoms is variable and treatment effects are dubious. In this mini-review, we discuss the most troublesome uncertainties that still surround HE, in the light of new data on etiology and epidemiology published in this issue of Neurogastroenterology and Motility.

KEYWORDS
hypercontractile esophagus, jackhammer esophagus, nutcracker esophagus

1 | INTRODUCTION

According to the Chicago Classification (CC) version 3.0,[1] hypercontractile esophagus (HE), also known as jackhammer esophagus, is a motility disorder diagnosed when on esophageal high-resolution manometry (HRM) at least 20% of wet swallow-induced peristaltic sequences is hypercontractile, that is has a distal contractile integral (DCI) >8000 mmHg·cm·s. This manometric diagnosis can only be made within the context of a normal lower esophageal sphincter (LES) relaxation, that is when the integrated relaxation pressure (IRP) is below the upper limit of normal, and when there is no manometric evidence of diffuse esophageal spasm (DES), which is presently defined by premature contractions.[1] In the era of conventional manometry, a condition akin or similar to HE, named nutcracker esophagus, was defined by abnormally strong peristaltic contractions (mean amplitude >180 mmHg).[2] Whereas there is consensus on the HRM criteria of HE, the disorder is still fraught with uncertainties. What are its causes? How does it lead to symptoms? How can it be treated?

This issue of the journal contains three scientific papers that provide new information on prevalence and demographics of HE, on its association with symptoms, and on effects of treatment. In this mini-review, we will attempt to place the new findings in the context of the existing knowledge.

2 | EPIDEMIOLOGY

Hypercontractile esophagus, as defined by CC 3.0, has previously been reported to constitute 1.5%-3% of manometric diagnoses and is encountered more frequently in females and in those older than 60 years.[3,4] In this issue of the journal, Wahba and Bouin, of Montréal, Canada, present a meta-analysis of 38 published HE case series.[5] Eleven of these studies reported on findings in unselected patients referred for HRM, and in these, a pooled HE prevalence of 1.97% (95% CI: 1.39%-2.78%) was found and a mean age at diagnosis of 60.8 years. Sixty-five percent of HE patients was female. HE was

significantly more prevalent in patients who had undergone lung transplantation and in morbidly obese patients. These pooled prevalence figures are in line with those of a recent French multi-center study, also published in this issue[6], in which HE was diagnosed in 1.4% of the 16264 HRM tests performed and the mean age of the HE patients was 60.8 years. However, in the French series only 33% of the patients with HE was female. In short, HE, as diagnosed with HRM and CC 3.0, is rare.

3 | ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of HE is uncertain. While most cases of HE are idiopathic, hypercontractility can also occur in response to esophagogastric junction (EGJ) outflow obstruction, as was observed in animal and human studies in which hyperexcitability of the esophageal body was noted following EGJ relaxation impairment.[7,8] Other studies have shown that esophageal acid perfusion can induce multipeaked, repetitive, spontaneous, or simultaneous esophageal contractions.[9] Moreover, symptoms of GERD are reported by approximately 40% of patients with HE, but usually these symptoms do not improve with acid-suppressive medications.[3,10] Finally, certain drugs might be associated with esophageal hypercontractility. Opioids can impair LES relaxation, decrease distal latency, and increase esophageal contractile amplitude. In a retrospective review of 225 HRM studies in chronic opioid users, opioid-induced esophageal dysfunction was found to be present in 24% of the patients.[11] In another HRM study in opioid users, EGJ outflow obstruction and type III achalasia were more frequently observed when HRM was performed on medication than off medication, while diffuse esophageal spasm (DES) and HE had a similar incidence on and off medication.[12]

The pathophysiology of HE is thought to be related to an excess of cholinergic drive and temporal asynchrony of circular and longitudinal muscle contractions[13,14] and patients with nutcracker esophagus often have an increased esophageal muscle thickness.[15] Histopathologic changes have also been described in HE and, more in general, in spastic esophageal motor disorders. Lymphocytic inflammation in the proximity of the myenteric plexus has been demonstrated in 36% of DES patients and in 45% of those with nutcracker esophagus diagnosed with conventional manometry.[16] In muscular biopsies taken during peroral endoscopic myotomy (POEM) in patients with HE and nutcracker esophagus, localized eosinophilic infiltration of the muscle layer was found in 4 out of the 5 cases (eosinophilic esophageal myositis).[17]

4 | INVOLVEMENT OF THE LES

Several studies have evaluated manometric heterogeneity within HE, one type of which pertains to involvement of the LES. CC 3.0 acknowledges that esophageal hypercontractility can be limited to the esophageal body but that the hypercontractile process can also include the LES, or even be restricted to the LES.[1] For this reason, CC 3.0 allows inclusion of the EGJ in the calculation of the DCI. The clinical significance of a substantial contribution of the LES to an elevated DCI in patients diagnosed with HE is still uncertain. Whereas one study observed that dysphagia was invariably present in patients with "LES only" hypercontractility [18], another study found no difference in symptoms and outcome between patients with LES-dependent and LES-independent elevated DCI values.[19]

Another type of LES involvement in HE is constituted by EGJ esophageal outflow obstruction. Both in the Canadian meta-analysis[5] and in the French cohort study[6] published in this issue, EGJ outflow obstruction, as evidenced by an elevated IRP, was common in patients diagnosed with HE (24.1% and 10%, respectively).[5,6] In a landmark study by Roman and colleagues, the mean IRP was found to be significantly higher in non-multipeaked HE cases than in multipeaked (see below).[20]

Although the jury is still out on the LES contribution to HE, it is likely that not only our understanding of HE but also treatment selection will benefit from taking the LES contribution into account in future studies on HE.

Key Points

- HE, as defined by the Chicago classification, is a rare disorder that is associated with dysphagia and chest pain.
- The mechanisms through which the observed esophageal hypercontractility and the reported symptoms are linked are incompletely understood.
- The almost complete lack of sham-/placebo-controlled therapeutic studies and the benign natural course of the disorder should lead to a conservative approach in the management of patients with HE

5 | MULTI-PEAKED CONTRACTIONS

Another source of manometric heterogeneity in HE is constituted by variability in the morphology of the esophageal contractions. These can be single- or multi-peaked, with multi-peaked synchronous pressure waves making up for 82-88% of the vigorous contractions.[18,20] In about 50% of HE patients with multi-peaked contractions, the pressure peaks appear to occur in synchrony with respiration, in the other half the peaks are not respiration-related.[18,20]

Because the repetitive powerful activity of the esophageal body in a subgroup of patients with HE was felt to resemble that of a demolition hammer, the term Jackhammer Esophagus was introduced in version 2 of the CC. The term is now widely used as a synonym for HE. It should be borne in mind, however, that multipeaked or repetitive activity is not seen in all patients with HE and, thus far, does not form part of the manometric criteria for HE. Somewhat surprisingly, the presence or absence of multipeaked contractions is

not described in many of the recently published papers with "jackhammer esophagus" in their title, including those in this issue of the journal.

It has been reported that HE patients without the repetitive peak feature more often have a high IRP and impaired deglutitive EGJ relaxation than those with the feature.[20] When esophageal contractions in patients with HE are divided into a pre-peak and a post-peak phase, regardless of the presence or absence of multiple peaks, post-peak hypercontractility is associated with higher overall contraction vigor and higher dysphagia scores.[21,22]

Based on these observations, it seems wise to take esophageal pressure wave morphology into account in future studies on HE, to avoid lumping of repetitive and non-repetitive HE subtypes and not to use "jackhammer esophagus" as a *pars pro toto* term.

6 | ASSOCIATION WITH SYMPTOMS

As summarized in Table 1, many publications have reported on the prevalence of symptoms in cohorts of patients with HE.[13,18–20,23,24] As a group, patients with HE report a broad range of symptoms, among which dysphagia (32%-100%), chest pain (10%-52%), and reflux symptoms (17%-58%) are the most prominent. In this respect, the symptom regurgitation is a source of confusion in the literature on HE since regurgitation can be a reflux symptom as well as a symptom of impaired esophageal transit.

Roman et al. reported that in HE (defined by at least one contraction with DCI >8000) dysphagia was the dominant symptom, reported by 32/44 of the patients, followed by chest pain (5/44) and reflux symptoms (13/44)[20]. Herregods and coworkers observed that most of the patients with HE (n = 34, defined by at least two contractions with DCI >8,000) suffered from dysphagia (67.6%) and/or chest pain (47.1%). All patients who had an isolated DCI of the LES >2000 had dysphagia.[18] More recently, Quader et al. evaluated 113 HE patients, of whom 30 also had EGJ outflow obstruction. In the group without outflow obstruction (n = 83), perceptive symptoms (heartburn, chest pain) were the most common (73%), while in the group with outflow obstruction (n = 30) transit symptoms (dysphagia) were reported most frequently (72%).[23]

TABLE 1 Studies on the hypercontractile esophagus, diagnosed with HRM and the Chicago classification, published as full paper, in English, and containing data on symptom prevalence and/or treatment

				Symptoms				Treatment (if any)		
First author	Year	HE cases	CC	Dysphagia	Pain	Reflux Sx	Other	Drugs[a]	Surgical[b]	Improved
Roman[20]	2012	N = 44	1.0	73%	11%	29%	–	39%	5%	67%
Marjoux[24]	2015	N = 8	2.0	100%	38%	–	–	88%	–	71%
Jia[35]	2016	N = 8	3.0	100%	12%	50%	–	100%	25%	63%
Crespin[36]	2016	N = 2	2.0	–	–	–	–	–	100%	100%
Hong[37]	2016	N = 10	3.0	70%	–	40%	10%	100%	–	50%
Bechara[30]	2016	N = 4	3.0	75%	50%	50%	–	–	100%	100%
Herregods[18]	2017	N = 34	3.0	77%	47%	41%	29%	–	–	–
Al-Qaisi[38]	2017	N = 45	3.0	76%	44%	47%	–	38%	27%	90%
Huang[39]	2017	N = 12	3.0	50%	42%	58%	–	–	–	–
Schupack[28]	2017	N = 40	3.0	48%	35%	35%	20%	22%	5%	73%
Kristo[3]	2018	N = 37	3.0	54%	35%	54%	–	78%	-	7%
Albers[29]	2018	N = 6	3.0	–	–	–	–	–	100%	100%
Quader[23]	2019	N = 83	3.0	59%	52%	46%	–	–	–	–
Kahn[19]	2019	N = 81	3.0	62%	47%	43%	–	79%	–	72%
Xiao[22]	2019	N = 38	3.0	58%	10%	32%	–	–	–	–
Mion[32]	2019	N = 12	3.0	–	–	–	–	–	75%	–
Clément[4]	2019	N = 36	3.0	72%	36%	42%	33%	–	-	–
Nabi[40]	2020	N = 10	3.0	–	–	–	–	–	100%	83%
Csucska[41]	2020	N = 28	3.0	32%	25%	32%	-	–	-	–
Bernardot[31]	2020	N = 13	3.0	–	–	–	–	–	100%	–
Woo[42]	2020	N = 42	3.0	52%	24%	17%	7%	–	–	–

Abbreviation: CC, version of Chicago classification.

[a]Proton pump inhibitors, antidepressants, anticholinergics, botulinum toxin injection, calcium channel blockers, fluticasone, phosphodiesterase inhibitors, nitrate/calcium channel blockers, peppermint oil, hyoscyamine, buspirone.

[b]Including POEM.

In the Canadian meta-analysis published in this issue, dysphagia, regurgitation, heartburn, and chest pain were found to be the most commonly reported symptoms (64.1%, 38.5%, 33.8%, and 30.7%, respectively),[5] and in the French multi-center study, the most frequent symptoms were dysphagia, regurgitation, chest pain, and heartburn (74.6%, 37.1%, 27.4%, and 19.9%, respectively).[6] Clearly, dysphagia is the symptom that brings patients with HE to the doctor most often.

At first glance, it is not easy to understand how the dysphagia associated with HE could be brought about by abnormally powerful but peristaltic esophageal contractions. Recent observations suggest, however that, whereas the onset of the pressure waves may be peristaltic, subsequent peaks often propagate in a chaotic fashion, and that an increased "chaotic ratio" is associated with higher dysphagia symptom scores.[21,22]

To accept a cause–effect relationship, a correlation between contractile vigor and presence or severity of dysphagia would help. For this reason, various studies have attempted to link higher contraction vigor to more frequent or more severe symptoms (both dysphagia and chest pain).[13,25,26] For instance, a study carried out with conventional manometry evaluating the relationship between contraction amplitudes and pain perception threshold on balloon distension studies demonstrated that the higher the contraction amplitudes, the lower the pain perception threshold, and the higher the pain perception.[27] In the cohort study by Philonenko et al.[6] published in this issue, the subgroup of patients who complained of dysphagia had a slightly but significantly higher median DCI than the subgroup who did not have dysphagia (11,802 vs 10,667 mmHg·cm·s). Statistically significant correlations between DCI values and presence and/or severity of dysphagia have also been found in a few earlier studies.[18,25] However, the observed correlations between dysphagia and esophageal hypercontractility observed in these studies are relatively weak.

Thus, although most patients with HE have symptoms of dysphagia, chest pain or heartburn, and their manometric abnormalities are unmistakable, we have difficulties linking these symptoms with esophageal hypercontractility on a group level. In an individual patient, it is usually impossible to prove that the symptoms are caused by abnormally strong esophageal contractions. This forms an obstacle in the management of patients with HE.

7 | TREATMENT

In symptomatic patients diagnosed with HE, good communication and reassurance are an important part of management. However, additional therapy is often desired. Potential treatment options include drugs (e.g., PPIs, smooth muscle relaxants, antidepressants), botulinum toxin injection, pneumatic dilation, and peroral endoscopic myotomy (POEM). Overall, there is limited evidence for the efficacy of treatments for HE. Randomized and placebo- or sham-controlled therapeutic studies are virtually non-existent. Furthermore, all reported positive results of uncontrolled therapeutic trials and cohort observations in HE should be seen in the light of the favorable spontaneous evolution of the symptoms. Schupack et al.[28] described the long-term outcome of 40 patients with HE, 56 subjects with EGJ outflow obstruction, and 33 controls. The majority of HE patients and patients with EGJ outflow obstruction showed clinical improvement or symptom resolution at a mean follow-up of 2.8 years, without medical or procedural intervention in the majority (72.5%). Specifically, 73% of the HE patients reported improvement after a mean follow-up of 36 weeks. Symptom persistence at follow-up was predicted by maximum DCI and IRP in both EGJ outflow obstruction and HE.[28]

The design of the Canadian meta-analysis and the retrospective French multi-center cohort study published in this issue was such that reliable conclusions regarding the effects of therapy on symptoms could not be drawn. The Canadian meta-analysis describes the treatment outcomes as "generally satisfactory", the French multi-center study as "disappointing".[5,6] The impression that "medical treatment seemed inferior to endoscopic treatment"[5] might be brought about by a greater placebo effect associated with more invasive procedures.

Whereas POEM is likely to reduce esophageal body contractility, it should be borne in mind that its effects in terms of symptom reduction in patients with HE were only evaluated in a few uncontrolled studies in small cohorts. The success rates in these series are high, up to 100%. In a cases series study by Albers et al, patients with non-cardiac chest pain likely due to esophageal hypercontractility including type III achalasia (n = 7), HE (n = 6), and DES (n = 1) were found to respond clinically to POEM.[29] Bechara et al published a report on POEM effect in 4 patients with HE.[30] When the LES was included in the endoscopic myotomy, patients had resolution or significant improvement of symptoms. In one patient who was treated with LES-preserving myotomy, resolution of chest pain was observed but significant dysphagia and regurgitation developed. Subsequent repeat POEM including the LES resulted in symptom resolution. In a recent publication, Bernardot et al. reported on the efficacy of POEM in 30 patients with non-achalasia esophageal motor disorders, 13 of whom had HE, the other 17 patients were diagnosed with nutcracker esophagus or DES.[31]. In this mixed group, the 3-month and 6-month symptom response rates were 100% and 87%, respectively. The importance of a sham- or placebo-controlled study design is underlined by the results of a randomized sham-controlled botulinum toxin injection trial carried out by Mion et al.[32] In this study that included 23 patients with HE, there was no difference in symptom improvement, as assessed by the Eckardt score at 3 months, between patients who received Botox and those who were in the sham-control group. Patients in both groups reported symptom improvement, suggesting a relevant placebo effect in both treatment groups.[32]

A third paper published in this issue of the journal describes a patient in whom dysphagia and manometric signs of HE resolved immediately after radiofrequency ablation for atrial fibrillation[33] The authors speculate that damage to extrinsic nervous fibers (vagus nerve branches?) and perhaps even to the myenteric plexus affected the balance between excitatory and inhibitory signals. Before we

start hoping that this observation might open doors to a new treatment modality, it should be noted that in an earlier case report a patient was described who *developed* HE after radiofrequency ablation.[34] Apparently, subtle variants of unintended nerve damage can lead to opposite results. Again, we must conclude that our understanding of the pathophysiology of HE is still insufficient.

It is clear that we need to understand HE better in order to improve our therapeutic achievements. In particular, we lack sufficient insight into—1—what causes the motor abnormality that we call HE and—2—how do the motor abnormalities (powerful peristalsis, multipeaked simultaneous waves, LES hypertension and dysrelaxation) lead to symptoms such as dysphagia and chest pain?

8 | KNOWLEDGE GAPS AND SUMMARY

Despite valuable new contributions to our knowledge and understanding of HE, including those that were published in this issue, troublesome uncertainties continue to surround this rare and apparently heterogeneous disorder. Whereas it is positive that there is global consensus on the manometric criteria for HE and that HRM allows assessment of manometric phenotypes better than conventional manometry, it can argued that the field has not progressed much since the era of the nutcracker esophagus diagnosed with conventional manometry. Etiology, pathophysiology, and symptom generation in HE remain incompletely understood. In addition, we suffer from a paucity of well-designed therapeutic studies. Invasive and irreversible treatment modalities, such as POEM, should not be regarded as state of the art until prospective studies, preferably sham-controlled, with sufficiently long follow-up, have proven their efficacy. We should proceed with caution.

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AUTHOR CONTRIBUTIONS

ES and AS both reviewed the literature and wrote the manuscript.

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