Advances in Management of Esophageal Motility Disorders
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Abstract
Esophageal manometry is an important tool for evaluating esophageal function. It can be used for assessing the esophageal peristaltic pattern and also peristaltic intensity. Additionally, lower esophageal sphincter (LES) function can be studied simultaneously. This information allows clinicians to thoroughly investigate patients presenting with esophageal and/or respiratory symptoms without identifiable structural cause. At present, high resolution manometry (HRM) is preferred over conventional manometry as it informs the result in pressure topography. These data correlate more precisely with the clinical presentation of patients with esophageal dysmotility. Consequently, the HRM working group has proposed the criteria known as Chicago classification to categorize and specify the esophageal motility abnormality based on the results from HRM. This article describes esophageal motility disorders according to the current diagnostic criteria and also how to manage them in brief.

Keywords: esophageal manometry, esophageal motility disorder

Esophageal motility disorders are often a neglected condition. Not only do the non-specific clinical presentations such as, heartburn, chest pain and chronic cough frequently overlap with the other common diseases, but there is also a lack of equipment for testing the esophageal function.

Esophageal motor function used to be evaluated by conventional manometry exhibiting the results in line tracing. In 2001, Spechler and Castell1 proposed applying these data for categorizing esophageal manometric disorders into 4 groups:
1. Inadequate lower esophageal sphincter (LES) relaxation that could be classic achalasia or atypical disorders of LES relaxation.
2. Uncoordinated esophageal body contraction referring to diffuse esophageal spasm.
3. Esophageal hypercontraction which may occur at body (nutcracker esophagus) or LES (hypertensive LES).
4. Esophageal body hypocontraction meaning ineffective esophageal motility (IEM).

In 1991, Clouse et al,2 started creating topographic esophageal plots from a conventional manometric study, and revealed more diagnostic accuracy for esophageal dysmotility.1 During the DDW meeting of 2007 in San Diego, the high resolution manometry (HRM) working group first collaborated to adjust esophageal pressure topography (EPT) to assess clinical esophageal dysmotility. In 2008, Kahrilas et al.4 published the first Chicago classification (CC) using esophageal pressure topography for diagnosing esophageal motility disorder, and later in 2012 and 2015 CC version 2.0 and 3.0 were announced, respectively.5,6

According to CC version 3.0, esophageal dysmotility is mainly classified into:
1. Poorly relaxing LES which could be achalasia or esophagogastric junction (EGJ) outflow obstruction.
2. Major disorders of peristalsis: absent contractility, distal esophageal spasm or jackhammer esophagus and
3. Minor disorders of peristalsis: IEM or fragmented peristalsis.6 Hypotensive (end expiratory resting LES pressure < 10 mmHg
Achalasia

Idiopathic achalasia is a primary esophageal disorder characterized by loss of esophageal peristalsis and impairment of LES relaxation. Approximately 3-4% of patients with suspected achalasia will be pseudoachalasia, a condition occurring when malignant cells are infiltrating and destroying myenteric plexus of distal esophagus or EGJ. Idiopathic achalasia is a rare disease. The incidence is 0.3-1.63 per 100,000 adults per year, and prevalence is 8.7-11.2 per 100,000 adults in 10 years.

Pathogenesis of achalasia is the impaired function or loss of postganglionic inhibitory neurons in myenteric plexus, which supply smooth muscle of distal esophagus and EGJ by secreting two neurotransmitters: vasoactive intestinal polypeptide (VIP) and nitric oxide (NO). Cytotoxic lymphocyte and/or complement activation may cause this chronic ganglionitis, especially in patients with HLA DQA1*0103 and HLA DQB1*0603 alleles. Some viruses for instance, herpes simplex virus-1 (HSV-1), measles, human papillomavirus (HPV) and varicella zoster virus (VZV) have been hypothesized to be involved in the pathogenesis of idiopathic achalasia. However, no study has firmly defined this association.

Clinical manifestations of idiopathic achalasia presumably correlate with the degree of esophageal pathology. Initially, patients with esophageal myenteric neuritis or ganglionitis predominantly present with vigorous achalasia (type III achalasia). Subsequently, when the inflammatory process resulting in a loss of ganglion cells and neural fibrosis, patients will finally develop classic achalasia (type I) or achalasia with compression (type II).

More than 90% of patients with achalasia present with dysphagia of solid and liquid. Other symptoms are heartburn, regurgitation of undigested food, non-cardiac chest pain and weight loss. Additionally, respiratory symptoms, such as hoarseness, sore throat, cough and pulmonary aspiration can also be found in patients with achalasia.

Esophagogastroduodenoscopy (EGD) should be performed in patients with dysphagia for ruling out mechanical obstruction; however, the sensitivity is low for diagnosing achalasia, especially in the early stage. The EGD findings that can be found in achalasia are dilated or tortuous esophagus, retained food in esophageal lumen, esophageal candidiasis and some resistance when passing the gastroscope through the EGJ.

Barium esophagography also has low sensitivity for determining the early stage of achalasia. Esophageal dilation and bird-beak appearance may be found in idiopathic achalasia.

Cautiously, if the length of distal esophageal narrowing is greater than 3.5 cm and proximal esophageal dilation is less than 4 cm, the physician should be suspicious of pseudoachalasia.

According to the current CC version 3.0, achalasia is classified into 3 types. The criteria for diagnosing type I achalasia is impaired EGJ relaxation [a median of integrated relaxation pressure (IRP) > 15 mmHg for HRM of Medtronic, Minneapolis, MN, USA] with 100% failed peristalsis [a swallow with distal contractile integral (DCI) < 100 mmHg-cm or DCI < 450 mmHg-cm with distal latency (DL) < 4.5 s]. If the patients also have panesophageal pressurization (more than 30 mmHg of pressurization extending from upper to lower esophageal sphincter) with at least 20% of swallows, they will be type II achalasia. For achalasia type III, HRM finding is impaired EGJ relaxation (median IRP > 15 mmHg), premature contraction (a swallow with DCI > 450 mmHg and DL < 4.5 s) with at least 20% of swallows without normal peristalsis.

The aim of treatment in achalasia is reducing the relaxing LES pressure to maintain esophageal structure and function. The brief conclusion of management is shown in Figure 2.
**Esophagogastric junction (EGJ) outflow obstruction**

EGJ outflow obstruction is esophageal dysmotility presenting with poorly relaxing EGJ when the criteria for diagnosing achalasia is not met (Figure 3). This condition used to be named atypical disorders of LES relaxation analyzed by conventional manometry. CC mentioned this condition as incomplete deglutitive EGJ relaxation in the first version, and changed to EGJ outflow obstruction in the latest 2 versions.

Definitive cause (i.e. primary or idiopathic EGJ outflow obstruction) cannot be found in approximately 70% of EGJ outflow obstruction. The rest of this condition (secondary EGJ outflow obstruction) might be caused by early stage or variant of achalasia, malignant infiltration at distal esophagus, peptic stricture, esophageal web or ring, eosinophilic esophagitis, hiatal hernia, medication such as opioids, and iatrogenicity such as fundoplication and gastric banding. There is a predispondance of idiopathic EGJ outflow obstruction in females (approximately 80%); however, about 50% of the secondary form is found in females. Mean age at diagnosis of both conditions is around 55 years-old.

The clinical presentation of EGJ outflow obstruction is dysphagia, chest pain, regurgitation, heartburn, weight loss, epigastric pain, and cough. HRM finding in this condition is suboptimally relaxing LES (a median of IRP > 15 mmHg for HRM of Medtronic, Minneapolis, MN, USA) together with preserved intact esophageal peristalsis. The symptoms of 19-40% of patients with idiopathic EGJ outflow obstruction improve spontaneously without any treatments. Some publications reported the benefit of botulinum toxin injection or esophageal dilation in this condition. Importantly, if the symptoms and signs of patients could not be explained by this condition,
Distal esophageal spasm (DES)

In 1889, Osgood\(^3\) first described the clinical presentation of DES. In 1934, the first radiographic finding of DES was reported by Moersch and Camp.\(^3\) In 1958, Creamer et al.\(^3\) were the first to demonstrate the manometric features of DES. DES is an uncommon condition. Merely 4-10% of adult patients undergone conventional esophageal manometry in tertiary care,\(^3\)\(^2\)\(^3\)\(^4\) and 2% of HRM test in patients with dysphagia had manometric feature of DES.\(^3\)

The pathogenesis of DES is still unclear. The deficit of the neural inhibition of the esophagus may lead to spastic peristalsis. There was evidence showing that nitric oxide can alleviate esophageal spasms, and also nitric oxide blockade can drive esophageal simultaneous contraction.\(^3\)\(^5\) GERD is prevalent in 38-64% of patients with DES.\(^3\)\(^2\)\(^3\)\(^4\) Recent CC (version 3.0) has defined the DES criteria as swallows with normally relaxing LES and premature contraction (a swallow with DCI > 450 mm Hg-s-cm with DL < 4.5 s) (Figure 4) with at least 20% of swallows.\(^4\) Some swallows with normal peristalsis may be seen in patients with DES. Contractile front velocity was used to establish premature esophageal contraction,\(^4\)\(^\text{5}\) but in 2011, Pandolfino et al.\(^3\) demonstrated that short DL was more accurate for identifying premature contraction than rapid contractile front velocity (CFV). Therefore, CFV has already eliminated the significance in the current version of CC.\(^4\) According to high prevalence of GERD in patients with DES as mentioned above, 24-h esophageal pH monitoring should be studied in patients with this esophageal dysmotility.

EGD offers a low yield to diagnosis of DES but it helps ruling out structural esophageal problems in patients presenting with chest pain or dysphagia. Cockscrew or rosary bead appearance may be found with a barium esophagography in DES; however, this finding is detected in only 4-14%.\(^3\)\(^2\)\(^4\) Figure 3: Demonstration of esophageal HRM findings (Medtronic, Minneapolis, MN, USA) of EGJ outflow obstruction. Suboptimal relaxing LES is noted and esophageal body peristalsis still preserves.

Around 73% of patients with DES present with retrosternal pain or dysphagia.\(^3\) The most common presentation in patients with DES is dysphagia, which found in 51%. Non-cardiac chest pain can be found as a leading symptom in 29%.\(^3\)

Figure 3: Demonstration of esophageal HRM findings (Medtronic, Minneapolis, MN, USA) of EGJ outflow obstruction. Suboptimal relaxing LES is noted and esophageal body peristalsis still preserves.

Figure 4: Demonstration of esophageal HRM findings (Medtronic, Minneapolis, MN, USA) of premature contraction. Swallows with greater or equal to 20% of premature contraction suggest of distal esophageal spasm (DES)
In patients with DES who also have concomitant GERD, the first line of treatment should be proton pump inhibitor. Calcium channel blockers, such as nifedipine and diltiazem may be of benefit for reducing chest pain and dysphagia in patients with DES who have no GERD. The study of antidepressants including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in patients with non-cardiac chest pain showed an advantage for these patients. Moreover, there was evidence showing that trazodone 50-150 mg/day can relieve chest pain in patients with DES. Endoscopic botulinum toxin injection in patients with non-achalasia, non-reflux spastic esophageal dysmotility including DES was beneficial, although there was recurrence in some of them during the follow-up. Pneumatic balloon dilation was shown to be beneficial in patients with DES who also had LES dysfunction. Furthermore, esophageal dilation was exhibited more valuable in DES patients who did not have concomitant GERD compared to those who had. Surgical myotomy is preserved for patients with DES who do not respond to initial treatment. It is recommended that fundoplication should also be carried out to prevent post-myotomy GERD. However, a suitable type of fundoplication performed to be less interfering with the esophageal bolus transit has not yet been well defined.

**Figure 5:** Algorithm for the management of distal esophageal spasm
Hypertensive contraction (nutcracker esophagus) and Hypercontractile (jackhammer) esophagus

In 1977, Brand et al.,52 reported patients with angina-like chest pain who had no coronary artery disease but presented high-amplitude esophageal contraction. In 1979, Benjamin et al., 53 reported high esophageal contraction pressure by manometry in patients with chest pain with or without dysphagia, and named this condition as nutcracker esophagus.53 In patients with non-cardiac chest pain, nutcracker esophagus can be found in up to 48% of cases.33

Nutcracker esophagus can be found in 6.4% of patients who have undergone conventional esophageal manometry. 54 From all of the patients who performed HRM study, this condition and jackhammer esophagus can be found in 2.3% and 0.06% of cases, respectively.38 Approximately 63-69% of patients with nutcracker esophagus are female. The mean age of patients at the diagnosis of nutcracker esophagus is 50-62 years-old. Around 33-70% of patients with this esophageal dysmotility also have concomitant GERD.39, 54, 55

The HRM working group proposed to increase this cut-off to 20% in version 3.0. There was evidence showing asynchrony between longitudinal and circular esophageal muscle in patients with nutcracker esophagus.57 This asynchrony could be reversed by atropine injection, therefore a hypercholinergic state may play an important role in this condition.58 Moreover, multipeaked esophageal contraction commonly seen in patients with jackhammer esophagus is also common in diabetic patients with peripheral and autonomic neuropathy.59 Taken together, these findings indicate that the imbalance of esophageal nervous supply may be one of the important factors in the pathogenesis of this esophageal hypercontractility. Reflux symptoms of up to 77% can be seen in patients with nutcracker esophagus55 and GERD can be prevalent 43% in jackhammer esophagus defining by CC version 3.0;66 however, it is still uncertain if GERD shares a causative role.

Thirty-one percent of patients with nutcracker esophagus have chest pain, and 21% of them have dysphagia.55 Some of them may present with reflux symptom or epigastric pain.55 One-fifth of patients with nutcracker esophagus present with more than one complaint.35 For jackhammer esophagus, the most common presentation is dysphagia (86%) whilst chest pain can be found in 67% and reflux symptoms including acid regurgitation and heartburn can be found in 52% and 45%, respectively.56

Richter et al.60 showed that the mean and standard deviation of distal esophageal pressure in 95 healthy subjects from conventional manometry were 99 mmHg and 40 mmHg, respectively. Therefore, initial criteria for diagnosing nutcracker esophagus from conventional manometry is swallows with a mean of distal esophageal amplitude greater than 180 mmHg.61 Moreover, the later study showed that the increased cut-off value of distal esophageal amplitude to 220 mmHg or 260 mmHg for establishing nutcracker esophagus yielded more clinical significance.42 From the HRM study in 75 healthy volunteers, the 95th percentile of mean of DCI is 5,000 mm Hg-s-cm.63 Consequently, the first two versions of CC defined nutcracker esophagus as: swallows with the mean of DCI more than 5,000 mmHg-s-cm.4,5 In 2012, Roman et al.64 showed the greatest value of DCI in any swallow from 72 healthy controls was 7,732 mmHg-s-cm. Therefore, CC version 2.0 established patients with a DCI greater than 8,000 mmHg-s-cm (Figure 6) with at least 10% of swallows was jackhammer esophagus, and of clinical relevance.6 Furthermore, nutcracker esophagus defined by the mean DCI greater than 5,000 mmHg-s-cm was already removed from the recent CC because this value can also be observed in control subjects.9 Achem et al.,65 informed the efficacy of acid suppression therapy in non-cardiac chest pain patients with GERD and nutcracker esophagus. More than 80% of patients reported an improvement of their chest pain, but esophageal manometry studies were normalized in only 2% of them.55 However, a later study failed to show the effectiveness of the proton pump inhibitor in alleviating chest pain in both normal and abnormal esophageal acid exposure nutcracker patients.66 Nifedipine can reduce resting LES and esophageal contraction pressure in

Figure 6: Demonstration of esophageal HRM findings (Medtronic, Minneapolis, MN, USA) of hypercontractile contraction. Swallows with greater or equal to 20% of hypercontractile contraction suggest jackhammer esophagus.
patients with nutcracker esophagus; however the clinical benefit is unclear. On the contrary, diltiazem, another calcium channel blocker, can improve chest pain or dysphagia in patients with this esophageal dysmotility in small clinical trials. The benefit of nitrates and sildenafil on symptoms of patients with esophageal hypercontractility is still uncertain. Anxiety or depression can be found in up to 24% of patients with nutcracker esophagus. Moreover, other central sensitization syndromes such as irritable bowel syndrome and fibromyalgia are also common in this esophageal dysmotility. Therefore, neuropsychiatric factors may play a role in causing a patient’s manifestations. Some antidepressants exhibited the benefit of relieving symptoms in patients with non-cardiac chest pain. Endoscopic botulinum toxin injection alleviates dysphagia in a half of patients with non-achalasia esophageal dysmotility, including DES and nutcracker esophagus at 1 month. However, only 30% of all patients still remain in clinical remission at 1 year after treatment. Bougie esophageal dilation has also been shown to be effective in nutcracker esophagus, but this effect may be caused by the placebo response.

**Esophageal hypomotility**

Esophageal hypomotility documented by conventional manometry is previously defined as IEM. The criteria for diagnosing IEM by line tracing is hypocontraction in esophageal peristalsis of at least 30% of swallows. Esophageal hypomotility is peristalsis with a distal esophageal amplitude of less than 30 mmHg, or simultaneous contraction with an amplitude less than 30 mmHg, or failed or absent peristalsis. From CC version 3.0 in 2015, the international HRM working group classified esophageal hypomotility into a major disorder which is absent contractility, and a minor disorder which is either IEM or fragmented peristalsis.

IEM can be found in 20-58% of patients who have undergone an esophageal manometry test, and in 27-32% of patients with non-reflux non-obstructive dysphagia. In patients with GERD, IEM can be found in 19.6-73.5%. From CC version 2.0, weak peristalsis with large break (WPLB) defined by esophageal peristalsis showing large breaks with at least 20% of swallows can be found 34% in patients with chronic cough, and 12% in patients with heartburn. Furthermore, WPLB or weak peristalsis with small break (WPSB) can be found in 67% and 20% of patients with erosive reflux disease and non-erosive reflux disease, respectively. However, the recent CC has defined esophageal peristalsis with an abnormal amount of large breaks as peristalsis exhibiting large breaks of at least 50% with swallows, and named this condition as fragmented peristalsis. Therefore, the epidemiology of fragmented peristalsis is still unclear.

The pathogenesis of esophageal hypocontraction remains uncertain. Kim et al. reported that the myopathy and/or imbalance of choline acetyltransferase (ChAT) and nitric oxide synthase (nNOS) neurons might lead to esophageal hypomotility. This esophageal dysmotility is prevalent in patients with GERD. IEM found in GERD may be caused by direct injury of caustic refluxate to esophageal myenteric neurons. Furthermore, hiatal hernia found commonly in GERD can lead to esophageal tortuosity, and disturbs esophageal peristalsis. Aging process may contribute to physiologic esophageal motor deterioration, and result in ineffective esophageal contraction. Other conditions, such as scleroderma, diabetes mellitus, hypothyroidism, amyloidosis, alcoholism and multiple sclerosis can also contribute to this hypocontraction.

Patients with esophageal hypocontraction may present with dysphagia, odynophagia and reflux symptoms, including heartburn and regurgitation. However, the severity of these manifestations does not correlate with esophageal function. Additionally, esophageal hypocontraction is related to respiratory symptoms such as chronic cough.

The recent criteria for diagnosing absent contractility, IEM and fragmented peristalsis are based on CC version 3.0. Absent contractility is a condition exhibiting 100% failed esophageal peristalsis (Figure 7). IEM is esophageal contraction with at least 50% ineffective peristalsis (either failed or weak peristalsis (a swallow with DCI > 100 but < 450 mmHg-s-cm)) (Figure 7). Fragmented peristalsis is condition presenting at least 50% fragmented contraction (a swallow with DCI > 450 mmHg-s-cm and break > 5 cm length in the 20-mmHg isobaric contour) (Figure 7). All of these esophageal hypocontractility disorders must have normally relaxing LES.
At present, the management of esophageal hypotension for recovering esophageal peristalsis is still limited. The current treatment aims at dealing with concomitant GERD, which is commonly found in this motility disease. Lifestyle modification may increase esophageal bolus transit, and reduce esophageal acid exposure. Chewing food thoroughly, consuming liquid and semi-solid foods, drinking plenty of water and using carbonated beverages can advocate esophageal bolus transit and prevent bolus retention. Weight reduction, avoidance of immediate recumbent position after meal, head-of-bed elevation, left lateral decubitus position and avoidance of oily foods or high-calorie diets can help in reducing esophageal acid exposure and/or frequency of reflux symptoms. Furthermore, there are several studies showing that gum chewing can decrease esophageal acid exposure, and relieve reflux symptoms in patients with GERD.

Pharmacological treatment in patients with esophageal hypotension consists of acid suppression therapy, alginate forming intra-gastric raft inhibiting both acid and non-acid refluxes, and prokinetics such as domperidone, metoclopramide, macrolides and serotonin receptor agonist and/or antagonist. Fundoplication is an effective long-term treatment for preventing gastroesophageal reflux. Although patients with severe esophageal hypomotility should be cautious for this surgery, this condition is not an absolute contraindication. Furthermore, there is the evidence showing that fundoplication can improve esophageal function in patients with GERD and esophageal hypomotility.

In conclusion, esophageal motility disorders, including LES dysfunction and esophageal peristaltic abnormality are important conditions. However, they are often underdiagnosed because some clinical presentations overlap with GERD, which is more commonly found in daily practice. In addition, esophageal manometry is not widely available and general physicians may not be familiar with this advanced esophageal function test. Further investigation with esophageal manometry in patients with refractory esophageal symptoms (such as, heartburn, regurgitation and non-cardiac chest pain) and/or respiratory symptoms (such as, chronic cough) of unclear causes might reveal the unique esophageal dysmotility disorder. This could guide clinicians to choose the appropriate treatment for their patients.

References


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