Changes in the Treatment of Primary Esophageal Motility Disorders Imposed by the New Classification for Esophageal Motility Disorders on High Resolution Manometry (Chicago Classification 4.0)

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ABSTRACT

The Chicago Classification is the most used classification for primary esophageal motility disorders (PEMD). This classification was recently updated to the 4.0 version. This opinion piece focuses on the possible implications for the treatment of PMED determined by the new classification. Chicago Classification 4.0 included two new concepts for the diagnosis of achalasia: (1) type III achalasia diagnosis demands 100% absent peristalsis defined as either failed peristalsis or spasm; (2) “inconclusive diagnosis of achalasia” was added as a possibility. Both may decrease unnecessary treatment. Esophagogastric junction outflow obstruction, distal esophageal spasm, and hypercontractile esophagus were only considered clinically significant when correlated to supportive testing and relevant clinical symptoms and in the absence of gastroesophageal reflux disease. This may decrease the surge of treatment, especially peroral endoscopic myotomy, based solely on manometric diagnosis.

Keywords: Achalasia; Chicago classification; Esophageal manometry; Esophageal motility disorders; High-resolution manometry; Peroral endoscopic myotomy

Key Summary Points

- Chicago 4.0 is the new classification for esophageal motility disorders based on high-resolution manometry.
- Previous classification may have caused overtreatment of specific manometric patterns.
- Chicago 4.0 defined criteria for clinically relevant specific manometric patterns.

DIGITAL FEATURES

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INTRODUCTION

The first widely accepted classification for esophageal motility disorders based solely on esophageal manometry was compiled by Richter in 2001 [1]. High-resolution manometry (HRM) was not available at that time but, certainly, the most relevant studies on primary esophageal motility disorders (PEMD) were conducted based on this classification. High-resolution manometry (HRM) made motility testing much more agreeable to patients (quicker test and no need to move the catheter once in place) and physicians (more intuitive, quicker learning) [2] but it was fundamentally a gift for researchers. First, all knowledge acquired by conventional manometry could be replicated under HRM. Second, HRM plots were so agreeable to the eyes that researchers started to see things that were probably in the conventional manometry tracings but were not perceived [3]. Every change in color, every inflection, every point was considered a new manometric parameter and many terms and parameters soon populated the literature.

The Chicago classification was designed by (and owes its name to) two gastroenterologists at Northwestern University in Chicago (John Pandolfino and Peter Kahrilas) who were pioneers in the development of HRM. They tried to standardize the interpretation of HRM but a widely accepted consensus was only obtained for the 3.0 version when significant simplification was adopted [4]. This classification was recently updated to the 4.0 version [5] with remarkable changes in many concepts [6], which may alter the way PEMD are treated.

This commentary focuses on the possible implications for the treatment of PMED determined by the new classification for esophageal motility disorders on high-resolution manometry (Chicago Classification 4.0).

ACHALASIA

Achalasia is still defined by aperistalsis of the esophageal body and a failure of the relaxation of the lower esophageal sphincter (LES) in response to swallowing (measured by the integrated relaxation pressure, IRP) (Fig. 1). Esophageal body pressurization after swallows defined types from I to III. Chicago Classification 4.0, however, included two new concepts for the diagnosis of achalasia: (1) type III achalasia diagnosis requires 100% absent peristalsis defined as either failed peristalsis or spasm; (2) “inconclusive diagnosis of achalasia” was added as a possibility.

The new classification clarifies that cases with an elevated IRP, and intermittent peristalsis should be diagnosed as esophagogastric junction outflow obstruction (EGJOO). EGJOO treatment is more complex than achalasia, and it will be discussed later but this distinction between achalasia and EGJOO certainly will prevent unnecessary treatment [7]. Probably several cases have been diagnosed as achalasia when in fact they were not. For several authors, per oral endoscopic myotomy (POEM) is the preferred therapy for achalasia type III. Curiously, when some case series of POEM for achalasia are carefully reviewed, the rate of type III is incredibly high—up to 50% [8, 9], even though type III is the rarest form and present in around 15% of the cases [10, 11]. More curiously yet, the proportion of type III in Heller’s myotomy for achalasia never reaches this high rate of type III [12]. It is not known whether the cases previously called “vigorous achalasia” at the time of conventional manometry represent Chicago type III achalasia since the definition was based on simultaneous waves of > 37 mmHg amplitude [13] and thus some cases of type II would be included as well. Even with a more liberal definition, severe cases represented 10–40% of the total cases of achalasia [14]. Whether this high proportion of type III cases in POEM series is an overdiagnosis or referral bias is not known.

‘Inconclusive diagnosis for achalasia’ falls within three conditions according to Chicago 4.0: first, absent contractility with no appreciable peristalsis in the setting of IRP values at the upper limit of normal in two positions, with or without pan-esophageal pressurization in 20% or more swallows. Interestingly, no definition for “upper limit of normal” was provided, and “with or without” does not add to a decision process. Nevertheless, this inconclusion is based
on the lack of formal deficit in LES relaxation based on the IRP as a unique parameter. These cases have been previously studied. A normal IRP is not uncommon in untreated patients with achalasia. Vicentine et al. [15] showed that 57% of patients with Chagas’ achalasia and 17% of patients with idiopathic achalasia had a normal IRP. Moreover, surgeons are used to treating patients after failed endoscopic therapy, making the evaluation of the LES faulty and relying only on the presence of aperistalsis at the HRM combined with other tests and clinical presentation [7]. If the diagnosis is based on a careful work-up and not based solely on manometry, outcomes are not jeopardized by the lack of a normal IRP [16]. Again, surgeons showed that Heller myotomy brings dysphagia relief even if the LES basal pressure is under the maximum normal IRP [17] or after endoscopic treatment at the LES resulting in apparent normal relaxation [18]. We compare the esophagogastric junction flow to a door. If the door is locked, closed, or ajar, one cannot pass through it. The door must be completely opened. For others, a ‘normal’ IRP may represent a door just ajar.

A second situation for ‘inconclusive diagnosis for achalasia’ is evidence of appreciable peristalsis with changing position in the setting of a type I or II achalasia pattern in the primary position. Interestingly, there is no recommendation to study patients with initial diagnosis of achalasia in two positions. We believe that this situation may occur if achalasia was NOT diagnosed in the initial position. Since supine is usually the standard position, we believe that a different diagnosis was based on the sitting or upright position. In this case, gravity may accelerate the transit, and a premature wave may be misinterpreted as aperistalsis by inexperienced examiners. Previous studies conducted by experts did not show a difference for the diagnosis of achalasia based on position [19, 20].

The third situation for ‘inconclusive diagnosis for achalasia’ is an inconclusive diagnosis of type III achalasia including an abnormal IRP with evidence of spasm and evidence of peristalsis. These patients should be classified as EGJOO with spastic features, which may represent an achalasia variant.

Other authors have proposed achalasia variants that were not supported by the Chicago 4.0 version, such as the variants in the Rochester classification [21]. It is valid to mention that South American experts frequently quote an ‘indeterminate’ variant of achalasia [15]. These experts have the chance to study patients with a

Fig. 1 Achalasia subtype I with no pressurization during swallows. The elevated integrated residual pressure (IRP) differentiates the case from absent contractility.
positive serologic test for Chagas’ disease in patients without esophageal symptoms to find a large spectrum of motility alterations [22]. Whether this represents early motility changes prior to complete aperistalsis or just occasional findings commonly found in asymptomatic individuals [23] is not known.

Supportive testing is recommended in the setting of these variants or inconclusive diagnosis, which is not different from what has been advocated previously [24].

ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

The Chicago 4.0 classification states that “a manometric diagnosis of EGJOO must always be considered clinically inconclusive.” EGJOO should be considered clinically relevant only in the presence of: (1) an elevated IRP in supine and upright positions with evidence of peristalsis; (2) supportive investigations with other tests such as a barium swallow to document obstruction at the level of the gastroesophageal junction; (3) presence of chest pain and/or dysphagia (Fig. 2). This necessary update from version 3.0 including supportive testing and clinical correlation was fundamental to preventing overdiagnosis and unnecessary treatment since most individuals with a manometric picture of EGJOO are asymptomatic or have few symptoms which may often resolve spontaneously [25]. A surge in the indication of POEM for EGJOO was indeed seen after Chicago 3.0 [26–28]. These series apparently diagnosed EGJOO based mostly on manometric findings since supportive tests are not clearly mentioned and chest pain and/or dysphagia is not present in some patients. Surgeons, on the other hand, have been very cautious about surgical treatment for primary motility disorders apart from achalasia, particularly for functional obstructions at the level of the LES [29]. If we try again to correlate conventional manometry diagnosis with HRM, some cases of the previously named “hypertensive LES” could correspond to EGJOO. Patti et al. analyzed the results of the esophageal function tests in 3471 patients and diagnosed a primary esophageal motility disorder in 397 patients. Among these 397 patients only 2 had a hypertensive LES. After an extensive work-up, only one of the two patients underwent a myotomy with resolution of the symptoms [30]. In fact, we have showed that surgery for hypertensive LES should only be indicated in the presence of obstructive symptoms [31]. This shows that in the era prior to POEM when surgical therapy and endoscopic balloon dilatation of the cardia were the available forms of treatment, patients were extensively studied, carefully selected, and selectively treated. POEM as a new and attractive technology appears to lead to overtreatment as a consequence of the bright light of innovation [32]. In fact, the ethics of
the adoption of POEM as the standard treatment for motility disorders has been the subject of some previous papers [33, 33]. As a curiosity, Brazilian engineers take an oath saying that: “I swear that during my duty as Engineer I will not allow myself to be blinded by the bright light of technology, as I should not forget that I work for the benefit of humankind not for the benefit of the machine.” Hippocrates did not anticipate this in the medical oath.

**DISTAL ESOPHAGEAL SPASM**

Distal esophageal spasm is still defined manometrically by at least 20% of premature contractions with normal contractile vigor; however, clinically relevant diagnosis of DES requires both clinically relevant symptoms (dysphagia and/or chest pain) and a conclusive manometric diagnosis. Similar to EJGOO, Chicago 4.0 incorporated clinical evaluation to avoid overtreatment. Also parallel to EJGOO, POEM has been extensively indicated as treatment [34–36] while operative treatment (Heller’s myotomy) is parsimoniously used in very selected cases [37].

Another remarkable contribution of the Chicago 4.0 is to credit dysmotility to gastroesophageal reflux disease (GERD) (Fig. 3). PEMD must be only considered in the absence of GERD. This has been previously described [38] even though some authors, especially gastroenterologists, grouped the same manometric pattern in a single entity irrespective of the presence of GERD [39]. Moreover, the presence of the same manometric patterns found in PEMD does not affect outcomes for antireflux surgery [40].

Inconclusive diagnosis occurs with premature contractions and low contractile vigor as measured by the distal contractile integral (DCI) parameter. Conventional manometry classification [1] did not adopt waves amplitude for the diagnosis of diffuse esophageal spasm. Probably the contractile vigor is irrelevant for the diagnosis, which must be correlated to clinical complaints and supportive tests as described.

**HYPERCONTRACTILE ESOPHAGUS**

Hypercontractile esophagus is defined by excessive peristaltic vigor in at least 20 of the swallows. Jackhammer esophagus was considered a synonym in Chicago 3.0 but now jackhammer is considered a subset of the term hypercontractile esophagus only when repetitive prolonged contractions are present.

There are several contributions regarding hypercontractile esophagus. First, the fact that obstruction (either physiologic or mechanical) at the esophagogastric junction may lead to hypercontractile response was acknowledged. Thus, an obstruction must be ruled out before definitive diagnosis. Second, GERD must also be ruled out for the same reasons discussed at the distal spasm section. Third, similar to distal spasm, the pattern is clinically relevant in the presence of dysphagia and/or chest pain. Fourth, three different patterns were defined: single-peaked hypercontractile swallows, jackhammer, and hypercontractile swallows with a vigorous LES after-contraction (Fig. 4). These patterns still cannot be prognostic or tailor treatment because of the lack of studies mostly due to the rarity of the disease and recent definition.

Similar to other described PEMDs, POEM has been liberally used to treat hypercontractile esophagus [41] while surgery has been underused [37]. We showed that indications for surgery for nutcracker esophagus (probably most cases of nutcracker according to the conventional manometry classification correspond to hypercontractile esophagus) are the presence of obstructive symptoms and evidence of obstruction at the LES.

Finally, Chicago 4.0 tried to decrease overtreatment stating that “a cautious approach in terms of treating contractile vigor as an endpoint and advocated for conservative medical therapy before endoscopic or surgical interventions are considered.”
INEFFECTIVE ESOPHAGEAL MOTILITY AND ABSENT CONTRACTILITY

The criteria for absent contractility were not updated in Chicago 4.0.

The definition of ineffective esophageal motility was updated in the Chicago 4.0. The diagnosis demands > 70% ineffective swallows (previously 50%) or at least 50% failed peristalsis (novelty) including fragmented peristalsis as ineffective swallow not as a distinct disease (novelty).

Absent contractility and ineffective esophageal motility as PEMD (GERD, medication usage, or systemic diseases should be excluded) have no specific treatment. No effective pharmacotherapy exists, and dietary intervention and lifestyle changes are the only available resources [42]. We also refer patients to speech language pathologists to train forceful swallows even though there is still no scientific evidence behind the proposal, although a achalasia patients use this technique to pressurize the esophagus and facilitate esophageal clearance [43].

CONCLUSIONS

Chicago 4.0 has updated definitions that may correct overtreatment caused by previous classifications that considered specific manometric patterns as diseases based solely on manometric findings. The new classification defined clinically relevant diseases based on more discerning parameters that must be correlated to clinical symptoms and supportive testing besides the
exclusion of GERD that is logical to define an esophageal dysmotility as a primary disorder.

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FAMH: Conception and design, acquisition of data, drafting the article.
MGP: Conception and design, acquisition of data, drafting the article.
LMDG: acquisition of data, review for intellectual content, final approval of the version to be published.
FS: acquisition of data, review for intellectual content, final approval of the version to be published.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Fig. 4 Hypercontractile esophagus subtype single-peaked hypercontractile swallows. This form is no longer called jackhammer
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