Curr Gastroenterol Rep (2016) 18: 59
DOI 10.1007/s11894-016-0532-y

ESOPHAGUS (JO CLARKE, SECTION EDITOR)

Chicago Classification of Esophageal Motility Disorders: Applications and Limits in Adults and Pediatric Patients with Esophageal Symptoms

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Published online: 13 October 2016

Abstract The Chicago classification (CC) is most valued for its systematic approach to esophageal disorders and great impact in unifying practice for esophageal manometric studies. In view of the ever-growing wealth of knowledge and experience gained by the expanding use of high-resolution manometry (HRM) in various clinical scenarios, the CC is regularly updated. Its clinical impact and ability to predict clinical outcome, both in adults and pediatrics, will be further promoted by recognizing its current limitations, incorporating new metrics in its diagnostic algorithms and adjusting the HRM protocols based on the clinical question posed. Herein, we discuss the current limitations of the CC and highlight some areas of improvement for the future.

Keywords Esophagus · Manometry · Adults · Pediatrics · Chicago classification

Introduction

HRM has advanced the study of esophageal motor disorders by abolishing the pull-through technique employed in conventional water-perfused manometry and presenting the data captured in conceptually intuitive color pressure plots. The first Chicago classification (CC), published in 2008, proposed a classification of distal esophageal motility disorders based on a comprehensive study of 400 patients and 75 controls [1]. Notably, the CC was not intended to be a global classification system of the entire spectrum of esophageal disorders. The second CC followed in 2011 and further characterized distal esophageal disorders and peristaltic esophageal body abnormalities [2]. In 2015, the third version of CC (CC v3.0) further outlined the characteristics of esophagogastric junction outflow disorders alongside a clear distinction between major and minor disorders of peristalsis, with a simplified classification of hypomotility [3]. The CC v3.0 successfully applies a logical, three-tier, treatment-oriented approach [4]. In order of priority of top-down exclusion, the categories are as follows:

- Disorders of esophago-gastric junction (EGJ) obstruction, as defined by elevated integrated relaxation pressure (IRP)
- Disorders of peristalsis, subdivided into

  – Major (never seen in normal individuals)
  – Minor (patterns potentially seen in normal controls without symptoms)

The CC encourages uniform practice in HRM recording by setting out a standard protocol (ten water swallows of 5 ml each, in supine position). This uniformity allows for inter-center standardization of data obtained, which in turn streamlines the rapidly expanding knowledge base around esophageal motility disorders.

On the other hand, the full potential of HRM is just being realized outside the confines of the CC. This includes the study of disorders involving the entire esophageal length and in the pre- and post-operative settings, as well as in the pediatric population.

This review follows on from our group's 2011 discussion of CC v2.0 [5]. Here, we will describe limitations of CC v3.0

KN and JO contributed equally to the preparation of the manuscript. DS reviewed and edited the manuscript before submission.

This article is part of the Topical Collection on *Esophagus*

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drawing upon our own experience and highlighting recent advancements. Our discussion will also propose concepts for incorporation into future iterations of the CC, including post-surgical assessment, evaluation of pharyngeal dysfunction, and emerging metrics of clinical relevance involving HRM.

The Esophago-Gastric Junction (EGJ)

The EGJ performs two main functions: facilitating antegrade esophageal clearance while preventing gastroesophageal reflux. A robust EGJ assessment would ideally evaluate adequacy of these two functions. Thus, a major limitation of previous and current CCs is incomplete EGJ functional assessment. Firstly, the CC does not address antireflux barrier function [6]. Secondly, the solitary HRM parameter defined for use in determining impaired EGJ outflow—the IRP—does not always correlate with disease severity and treatment response [7, 8]. Subjects without obstructive symptoms may meet manometric criteria for EGJ outflow obstruction, as seen in 3 out of 34 patients in a 2015 study [8]. Equally, while normalization of IRP often does coincide with symptom resolution in treated achalasia [9], it is now apparent that the reverse does not hold true and that recurrent dysphagia correlates poorly with lower esophageal sphincter (LES) pressures [10••]. Clearly, EGJ relaxation as ascertained by the IRP is only one factor determining satisfactory bolus transit across the EGJ. A "normal HRM" in nonobstructive dysphagia should ideally be followed by functional evaluation of EGJ anatomy and distensibility to determine their influence on bolus flow dynamics. Future versions of the CC should consider addressing these shortcomings by incorporating relevant new HRM metrics and making reference to supplementary diagnostic techniques as described below.

Assessment of Antireflux Barrier Function

EGJ Contractile Integral (EGJ-CI)

The EGJ-CI was introduced in 2014 by Nicodeme et al. [11••] to quantify EGJ integrity based on inter-deglutitive EGJ pressures. The EGJ-CI has improved upon its conceptual predecessor, the LES pressure integral (LES-PI) [12], by minimizing the contribution of diaphragmatic contraction, and referencing intragastric as opposed to atmospheric pressure to correct for abdominal obesity.

One merit of the EGJ-CI is that it is technically ready for adoption within existing HRM setups. EGJ-CI calculations can already be performed within currently available HRM analysis software by forcing the DCI tool across the EGJ and over three respiratory cycles, then dividing the result by three (for each respiratory cycle) and then by the duration of the three respiratory cycles [13].

The EGJ-CI is potentially most useful in the diagnosis and management of gastroesophageal reflux disease (GERD), where the antireflux barrier is compromised by reduced pressures as a function of (in part) reduced contractility. Low EGJ-CI values have been shown to differentiate subjects with confirmed abnormal distal esophageal acid exposure from normal controls [11••]. Lower EGJ-CI values were also more predictive of PPI nonresponse [11••], improvement in reflux symptoms with antireflux surgery (ARS) [13], and decreased likelihood of new obstructive symptoms post-ARS [14].

The EGJ-CI also has conceivable utility as an objective perioperative outcome measure. An observational study of patients undergoing surgical intervention to the EGJ [15] described higher baseline EGJ-CIs in achalasia compared to GERD ($p < 0.001$) or normal controls. Achalasia patients post-myotomy recorded lowered EGJ-CI compared to baseline, reflecting improved bolus transit function, and the opposite was seen in GERD patients post-ARS.

Assessment of Esophageal Clearance

HRM on its own provides important but incomplete information regarding esophageal bolus transit. Here, we discuss the evidence supporting two diagnostic adjuncts, timed barium esophagogram and functional luminal imaging probe, to HRM for assessment of EGJ outflow.

1. Timed barium esophagogram (TBE)

The TBE is a quick, simple, noninvasive, and widely available means of quantifying esophageal clearance [16] and also illustrating anatomical deformity in the absence of other abnormal EGJ parameters.

The use of the TBE is reasonably well described in characterizing de novo diagnoses of achalasia [17, 18] and is particularly useful in revealing distal esophageal sigmoidization limiting esophageal emptying in the presence of low pressures. The best-established indication for TBE is in post-treatment monitoring of achalasia. Esophageal stasis at 5 min post-ingestion of barium has proven superiority to symptom assessment in predicting therapeutic failure at 1-month [19], 3-year [20], and 10-year follow-up [10••]. Furthermore, the lattermost study by Rohof et al. [10••] demonstrated no correlation between LES pressure and symptoms or height of barium column and echoed Richter et al.'s [18] recommendation of the TBE as the surveillance method of choice in post-treatment achalasia.

TBE has also been used as a complementary tool to evaluate nonachalasic EGJ outflow obstruction and esophageal dysmotility presenting with dysphagia [8, 21]. The clinical impact of TBE in these areas warrants further study.

2. Functional luminal imaging probe (FLIP)

EGJ distensibility refers to its ability to be distended or stretched under pressure [22]. The concept of EGJ distensibility as a major determinant of flow [23] has rapidly gained acceptance in the past decade as this directly accounts for the dynamic contributions of E-G pressure gradient and esophageal fibrosis on esophageal emptying [24].

Using the FDA-approved endoscopic functional luminal imaging probe (EndoFLIP®, Crospon, Galway, Ireland), volume-controlled balloon distensions across the EGJ are translated into intraluminal pressure and cross-sectional area measurements using high-resolution impedance planimetry. The resultant real-time topographic images are intuitive to interpret, with a less-distensible EGJ giving the FLIP bag an hourglass silhouette under volumetric distension. The "waist" of the hourglass, expressed in mm^2/Hg, has been defined by Pandolfino et al. as the EGJ distensibility index (EGJ-DI) [25•].

It is worth noting that EGJ distensibility was first validated in the settings of GERD [7] and post-fundoplication [26] and remains a valuable physiological endpoint for evaluating the latter, for example after different types of fundoplication [22].

Nonetheless, the main advantage of EGJ distensibility measurement appears to be in assessing treatment outcomes in obstructive diseases—compared to other metrics. EGJ distensibility has a better correlation with symptom severity in achalasia [24, 25•] and eosinophilic esophagitis [27]. Use of the FLIP is presently limited to major centers but is anticipated to follow the trajectory of HRM in being widely adopted as its clinical applicability becomes more evident.

The Esophageal Body

Distal esophageal spasm (DES) was previously diagnosed in the presence of simultaneous contractions of the distal esophagus and normal LES relaxation. In CC v2.0, the diagnosis of DES incorporated two metrics to account for peristaltic velocity and prematurity of onset, respectively: the contractile front velocity (CFV) and distal latency (DL).

The current CC has omitted the CFV and now defines DES as premature esophageal contractions (DL <4.5 s for ≥20 % of swallows) in combination with a normal IRP. This revised definition was based on Pandolfino et al.'s [28] retrospective study of 91 patients meeting CC v2.0 criteria for DES (high CFV and/or short DL), where short latency was discovered to be more specific for dysphagia and eventual treatment for DES, whereas patients with normal-latency rapid contractions (i.e., high CFV alone) were ultimately diagnosed with weak peristalsis or normal motility.

However, a 2015 Amsterdam case series shows that these subjects, with high CFV and normal DL, have an equivalent symptom burden and share many other manometric features with their short-latency counterparts [29••]. The group studied 23 patients with symptoms suggestive of DES who had a DL <4.5 s or a CFV >9 cm/s, or both. Based on these findings, they hypothesized that DES is part of a continuum whereas rapid contractions with normal latency represent the early stage of the spectrum and achalasia type III the most severe end. A recent case series demonstrating that 14 % of patients with DES progressed to achalasia at 2 years of follow-up supports this hypothesis [30].

In addition, a variety of nonstandard peristaltic morphology encountered on HRM in patients with esophageal symptoms remains unaccounted for in the current CC. The presence of multipeaked waves (MPWs) has been a subject of contention long predating the advent of modern HRM (Fig. 1). Some experts have suggested that MPW is a clinically relevant manifestation of defective esophageal inhibitory innervation that can be seen in diabetic autonomic neuropathy [31] and spastic motor disorders [32]. In contrast, Richter et al. found bipeaked waves in 11 % of normal subjects [33], and Sampath et al. explains MPW as respiration-related motion artifact [34]. A consensus opinion is required.

Other examples of aberrant morphology in symptomatic individuals include the merging of smooth muscle contraction segments and/or exaggeration of S3 (the distal third smooth muscle section of the esophagus) [35]. There is also no official CC designation for the phenomenon of "esophageal shortening" (Fig. 2), i.e., the rostral movement of the LES during deglutition caused by longitudinal muscle contractions [36], which is sometimes seen in noncardiac chest pain [37] and reflux symptoms [5, 38]. Further study of these nonspecific esophageal motor abnormalities is warranted to establish their clinical significance and allow uniform characterization within the CC algorithm (Fig. 3).

Finally, clinicians must be aware that current CC parameters may not accurately reflect post-surgical situations. Consequently, the CC overestimates normality of esophageal motility after iatrogenic disruption of smooth muscle fibers. This is singularly problematic when investigating recurrent chest pain or dysphagia after interventions for type III achalasia and hypercontractility disorders. Further management decisions must be based on careful HRM interpretation. A long Heller's cardiomyotomy to palliate esophageal spasm is typically 6–10 cm (median 8 cm) [39]. Per oral endoscopic myotomy (POEM) done for the same indication results in a median myotomized length of 16 cm [39, 40]—double the length of conventional POEM for achalasia types I and II [41, 42]—and may be even longer (up to 27 cm) [39] as determined by the proximal extent of hypercontractility

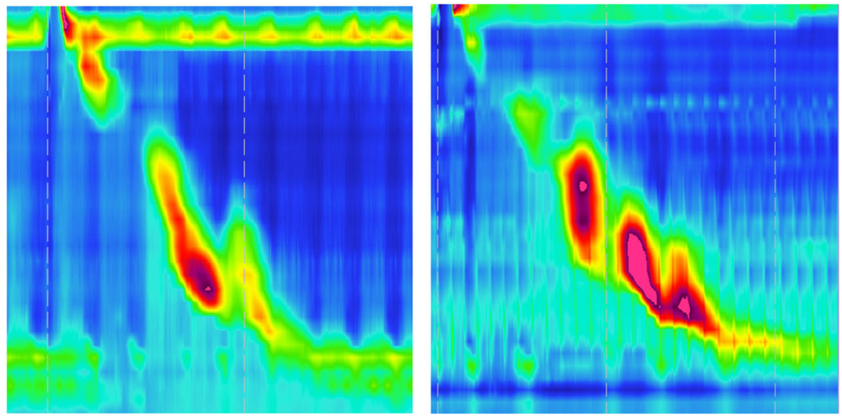

Fig. 1 Multipeaked waves (MPWs). Two examples of multipeaked peristaltic waveforms of normal DCI, which under CC v3.0 would be categorized as normal motility. While these appearances are frequently observed in patients with dysphagia, they have also been described in normal subjects as a consequence of respiratory artifact

visualized manometrically or on intraendoscopy [43]. An extended myotomy may still be insufficient to obliterate the entire spasmogenic area. A 2014 case report of POEM for Jackhammer esophagus described recurrent symptoms arising from post-operative residual spasm in a short proximal remnant of the esophageal body. Manometric measurements of this segment alone did not satisfy CC criteria for hypercontractility; nonetheless, the segment was treated with endoscopic balloon dilatation with good symptom resolution [44]. We have noted similar findings in our center (Fig. 4).

Provocative Tests

The physiological phenomenon described as deglutitive inhibition becomes more pronounced when multiple swallows are taken in rapid succession (where the esophageal body remains in inhibition until the last swallow is taken after which a full peristaltic contraction occurs) [45]. Multiple rapid swallowing (MRS) (5 liquid swallows—2 ml each—taken less than 4 s apart) and multiple water swallows (MWS) (free water drinking of 200 ml of water within 30 s) are the most commonly employed provocative tests, while solid boluses and test meals are also useful.

Post-MRS contractions are a good indicator of peristaltic reserve in the esophageal body [46]. The failure of post-MRS peristaltic augmentation seen in ineffective esophageal motility (IEM) offers a number of prognostic possibilities: it predicts failure of promotility agents [47], higher acid exposure time in nonerosive reflux disease [48], outlet obstruction following ARS [49] alongside potential benefit from dilatation thereafter [50], and persistence or development of IEM post-ARS [14]. Poor post-MRS contraction is also the commonest manometric finding in systemic sclerosis [51], even more so than the IEM seen in the textbook description of CREST syndrome. This is a vitally important diagnosis to exclude since GI symptoms are often the first manifestation of this life-limiting multisystemic connective tissue disorder [52].

The CC Working Group has acknowledged the value of the multiple rapid swallow challenge (MRS) in determining peristaltic reserve in the context of esophageal hypomotility [3]. Adopting the MRS into the CC-prescribed protocol is triply advantageous in that MRS is the most widely-studied provocative test [46, 50, 53], provides a computationally simple endpoint (peristaltic augmentation ratio post- versus pre-MRS) [51], and is quick and inexpensive to perform.

The multiple water swallow (MWS) test, or rapid 200 ml drinking challenge, is applicable to different situations. The most important clinical application of the MWS is in

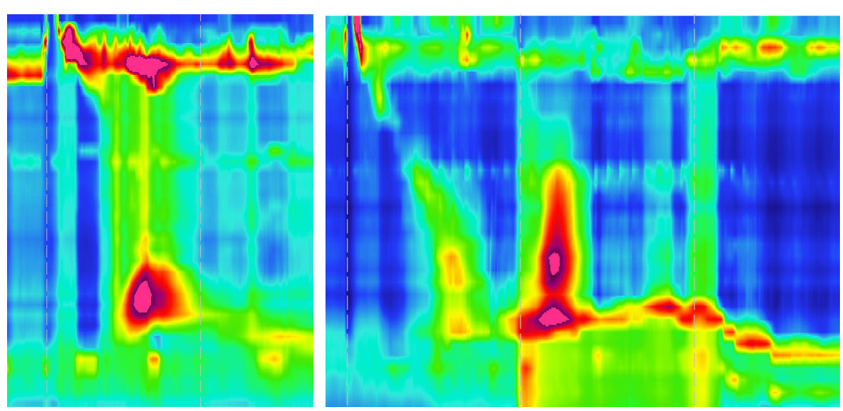

Fig. 2 Esophageal shortening. Transient lifting of the LES, coinciding with spastic contractions and symptoms of retrosternal hold-up and chest pain. This phenomenon is attributed to longitudinal muscle contractions

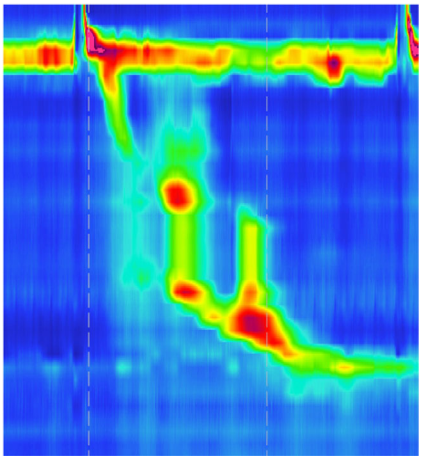

Fig. 3 Aberrant peristaltic morphology. Example of nonstandard peristaltic waveforms in a patient with dysphagia, whose HRM parameters meet CC v3.0 criteria for normal motility

distinguishing EGJ obstruction from achalasia. MWS in EGJ obstruction results in LES relaxation as deglutitive inhibition is intact (although a degree of esophageal pressurization may still occur if bolus clearance is exceeded by the rate of bolus delivery). In contrast, MWS in achalasia leads to sustained pressurizations along the entire esophageal body (panesophageal pressurizations) and exaggerates the existing large pressure gradient across a non-relaxed EGJ [54•]. Therefore, the use of MWS would be helpful in: i) detecting pan-esophageal pressurization in achalasia to support accurate subtyping; ii) identifying increased resistance to EGJ outflow, and iii) uncovering latent hypercontractility [54•]. This is particularly true where a standard 10-swallow HRM protocol is insufficient to reproduce typical obstructive symptoms and/or manometric abnormalities meeting CC criteria.

MWS offers evidence to support a diagnosis of erosive GERD. In terms of after-MWS response, effective peristalsis was seen in 83 % of healthy controls compared to 70 % of patients with non-erosive esophagitis and only 30 % of patients with erosive esophagitis [55]. Moreover, an abnormal MWS test is associated with the presence of GERD in patients who would otherwise be classified as having normal motility based on 10 single water swallows [56].

Challenges with viscous or solid boluses and test meals have also been proposed for use during HRM testing as they mimic esophageal pressures generated during normal drinking and eating. More than one pharyngeal swallow is usually required for complete solid bolus transport [57]. While normative values for manometric parameters with solid or viscous swallows have yet to be established, these tests are particularly helpful in evaluating dysphagia to solids when the standard protocol of 10 water swallows is insufficient to reproduce typical obstructive symptoms and/or manometric abnormalities meeting CC criteria. As seen with MWS, patients with erosive esophagitis fail to mount the appropriate augmented peristaltic response to the increased bolus consistency of a solid meal, which discriminates them from subjects without GERD or with non-erosive GERD [55]. Sweis et al. recently presented a 2-year outcome study of 18 patients who were investigated with HRM and a standardized test meal demonstrating that the manometric classification was altered based on the results of the test meal in 67 % of the cases and the clinical diagnosis and management was changed in 39 % [58•].

In summary, provocative testing should be widely incorporated into routine HRM protocols to improve diagnostic yield and provide treatment-altering prognostic information. The standardization and description of appropriate provocative

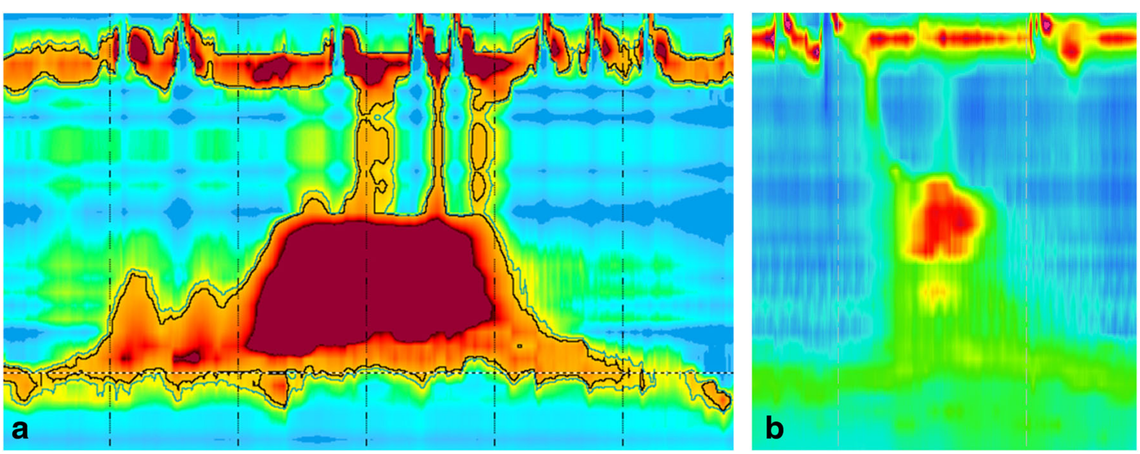

Fig. 4 Pre- and post-myotomy. **a** From the index HRM of a 23-year-old woman diagnosed with spastic achalasia (which would now be labeled achalasia type III under CC v3.0). She underwent a Heller's myotomy which afforded reasonable but incomplete symptom relief. Six years later, she re-presented with progressive dysphagia and chest pain. Her latest HRM (**b**) shows the source of her symptoms to be a remnant spastic segment above the myotomized length of the esophagus. Careful consideration of the patient's treatment history has prevented this HRM from being reported as unremarkable purely on the basis of meeting CC v3.0 criteria for normality

tests would be a welcome and timely addition to the CC. We propose that each HRM is accompanied by at least one of the tests described here to suit the clinical question posed.

Postsurgical assessment - Antireflux surgery (ARS)

Evaluation of esophageal symptoms post-antireflux surgery (ARS, interchangeable with fundoplication) is a common indication for HRM. For this reason, the description of a standardized approach building upon the proliferation of recently published normative and outcome data deserves a place in future versions of the CC. In current HRM practice, characterization of post-fundoplication status and function is a composite of three factors: i) EGJ anatomical configuration; ii) EGJ resting pressure and IRP; iii) esophageal body motility.

The post-ARS EGJ complex consists of the LES and the fundic wrap – which collectively constitute a manometric double high-pressure zone (DHPZ) – and the diaphragmatic crura. Manometric appearances corresponding to EGJ structural integrity in different post-fundoplication scenarios have been well described by Hoshino et al. [59]. Visual identification of a single DHPZ at the LES confirms appropriate fundoplication position. A single DHPZ that is normotensive and relaxes indicates normal fundoplication function. Post-ARS LES hypotension indicates wrap disruption whilst hypertension with incomplete relaxation means the fundoplication is likely to have twisted. A separated (dual) DHPZ usually suggests wrap slippage below the LES. Dysphagia in this context may be associated with hiatal flow resistance [60] (which can also explain ineffective transit in the non-operated hiatus hernia [61]).

Caution must be taken in HRM interpretation to identify the type of fundoplication performed. In asymptomatic post-ARS subjects with normal bolus transit, prospective data illustrate a clear difference in normal IRP values for the Toupet (270° partial posterior) fundoplication (upper limit of normal 15 mmHg with Given Imaging manometric systems), identical to standard CC v3.0 definition) versus the more restrictive 360° Nissen fundoplication (upper limit of normal 24 mmHg) [62]. That said, postoperative dysphagia is a significantly more common consequence of Nissen fundoplication compared to Toupet (RR 1.61) [63] and this may be related to higher IRP [64]. It may also be worth measuring HPZ length as a surrogate of effective wrap length: longer wrap length corresponds to increased likelihood of post-Nissen dysphagia [64, 65] whereas a shorter Toupet wrap (1.5 cm versus 3 cm) is associated with treatment failure and endoscopic recurrence of GERD [66].

Where baseline esophageal motility is normal, smooth muscle contractile vigor post-ARS is typically enhanced due to functional esophageal outlet obstruction arising from the fundoplication [14]. This effect is statistically more pronounced post-Nissen [62]. Normal post-ARS distal contractile integral (DCI) values have yet to be defined. However, a normal range of 20–30 mmHg for post-ARS IBP values has now been described, applicable to both post-Nissen and post-Toupet groups: this range sits between the cut-off value of 20 mmHg for untreated subjects and the 30 mmHg threshold seen in EGJ outflow obstruction with or without fundoplication [62].

Peri-ARS IEM is a more heterogeneous entity, but we now know that determining pre-operative peristaltic reserve is key to predicting and therefore optimizing surgical outcomes. In a retrospective study of 68 subjects with reflux and/or transit symptoms post-ARS, Gyawali et al. ascertained that a good after-MRS contraction on the pre-ARS HRM corresponded with resolution of pre-operative IEM. Conversely, poor post-MRS augmentation predicted development of new IEM in those with normal pre-operative motility, as well as post-ARS persistence of pre-existing IEM [14].

UES and Pharyngeal Assessment

One stark omission from the current CC is the lack of reference to pharyngeal and upper esophageal sphincter (UES) evaluation. Raw manometric data of the pharyngoesophageal segment is readily captured on routine esophageal HRM protocols – catheter length and positioning permitting – but this is very much an underutilized resource at present. The ability to systematically interpret this information would be of great value to GI specialists, as well as to healthcare professionals of all other disciplines involved in evaluating and managing pharyngeal disorders through the investigation of esophageal dysfunction in dysphagia, globus [67] and cough [68].

New data based on standard-issue esophageal HRM data acquisition and analysis software has just been published to address this unmet diagnostic need. Two prospective studies are proposing normal values for HRM metrics in asymptomatic subjects as validated against videofluoroscopy [69••, 70]. The study by Nativ-Zeltzer et al. [69••] is notable for introducing a novel system of manometric variables to appraise various components of pharyngoesophageal physiology and for deliberately recruiting older individuals (median age 74 years) to clarify age-related changes in pharyngeal function.

Pharynx-specific data acquisition protocols and customized research software [71, 72] have also been used extensively in the last decade to develop the clinical applications of pharyngeal HRM in otolaryngology as well as GI physiology [73]. The utility of standalone pharyngeal HRM has been established in discriminating normal from disordered swallowing [74, 75]. It has also been nonradiologically instrumental in addressing specific questions that will improve the target and design of swallowing therapies. Parameters examined include pharyngeal pressure topography shifts with different bolus volumes [76], various physical maneuvers [77–80], and manometric profiles in different disease states [81]. Other studies have aimed to stratify risk for penetration and aspiration [72] and post-swallow residue [82]. A new pilot case–control study in a post-total laryngectomy cohort seeks to understand the mechanisms of functional swallow production in these patients [83]. Concomitant impedance measurement, as pioneered by Omari et al., adds a new dimension to pharyngeal HRM by allowing the calculation of "admittance" in evaluating and prognosticating UES dysfunction [84–86].

The ultimate endpoint would be widespread clinical adoption of standardized and validated pharyngeal HRM techniques as an adjunct—or even alternative—to current modalities of swallow assessment by esophagologists, otolaryngologists, and speech pathologists [73, 87]. The metrics obtained may then form the foundation of a clinically relevant classification system of pharyngeal disorders, which would be equally valuable as a complement to the CC or as a standalone document.

High-Resolution Manometry and the CC in Children

Esophageal manometric evaluation is gaining ground in the pediatric world. The main indications for performing an esophageal manometry in children include esophageal dysfunction not explained by anatomic or other well-defined etiologies, presence of dysphagia and/or odynophagia, suspected diagnosis of achalasia or other primary motor disorders, and presence of gastroesophageal reflux (to exclude other pathology, locate the lower esophageal sphincter or prior to fundoplication) [88]. But, there are some unique considerations that need to be taken into account when one performs an esophageal manometric study in children [88–90].

Technical Considerations and Limitations of HRM in Children

Firstly, there are no normative values for pediatric patients that have been derived from a healthy population, as this is an invasive test. Thus, adult-derived values are currently being used for study interpretation [91]. Some investigators argue that there are HRM metrics that are more dependent than other parameters on the esophageal length and suggest that patient's age and size need to be accounted for. Goldani et al. have suggested adapting the DCI to the esophageal length as it is measured along the length of the esophagus between the transition zone and the LES [92]. The new metric (DCIa) was noted to be lower in children with peristaltic dysfunction, and the authors argue that this may be useful in the assessment of hypotensive peristalsis. Singendonk et al. [93•] found through linear regression analysis that higher IRP, shorter DL, and smaller peristaltic 20 mmHg isocontour break size (BS) correlated with younger age and shorter esophageal length. After adjusting for age and esophageal length, 47–48 % of the HRM studies analyzed demonstrated an esophageal motor disorder compared to the original 66 % if adult metric criteria were used. This highlights the possibility of overdiagnosing pathology in pediatric HRM. The authors propose that compartmentalized pressurization for the diagnosis of EGJ outflow obstruction, or rapid CFV for distal esophageal spasm, may need to be incorporated in the application of the CC criteria in pediatrics (this is also advocated in adults—see discussion above).

Secondly, the development and maturation of the gastrointestinal system needs to be taken into account when interpreting a study. The sequential pressure segments are recognizable at all ages with HRM, but at full term, only 55 % of swallows show a complete segmental chain with further development occurring in infancy [94, 95].

Lastly, there are some technical aspects that need to be considered. The age of the child determines the type of catheter size to be used. The development though of solid-state catheters for children has facilitated the transition from conventional manometry to high-resolution manometry; however, normative data utilized for adult populations may not apply to a pediatric-sized catheter. Moreover, the amount of fluid offered should be adjusted for age, with most investigators suggesting the use of 5 ml aliquots in children >5 years, 2 ml in children <5 years, and 0.5–1 ml in infants [90, 92]. The child's cooperation is also crucial during the study as this is best performed in an unsedated patient. Should sedation be required, midazolam and chloral hydrate have been shown to have minimal or no effect on the results of the study [96, 97].

Clinical Use of HRM in Children

In regard to achalasia in children, its diagnosis remains heterogeneous amongst centers. Some pediatric units are still diagnosing achalasia on the basis of symptoms, radiologic and endoscopic findings [98]. Access to pediatric HRM is limited to tertiary pediatric gastroenterology referral centers [99] while the lack of tolerance to the procedure by the child deters most physicians to refer. Treating clinicians, though, should consider the impact on treatment options when an accurate diagnosis is made with HRM with subclassification [100–102] (Fig. 5). For the diagnosis of achalasia in children, the CC criteria should be fulfilled but adjuvant metrics/findings need to be employed. This is due to the fact that normal IRP values are lacking in children and there might be heterogeneity in children's LES function [103]. Caution should be applied when considering previous studies using standard perfused manometry in the evaluation of LES function (as in the study mentioned above by Morera and Nurko [103]). It is now recognized that esophageal shortening and LES "pseudorelaxation" can lead to misinterpretation of EGJ

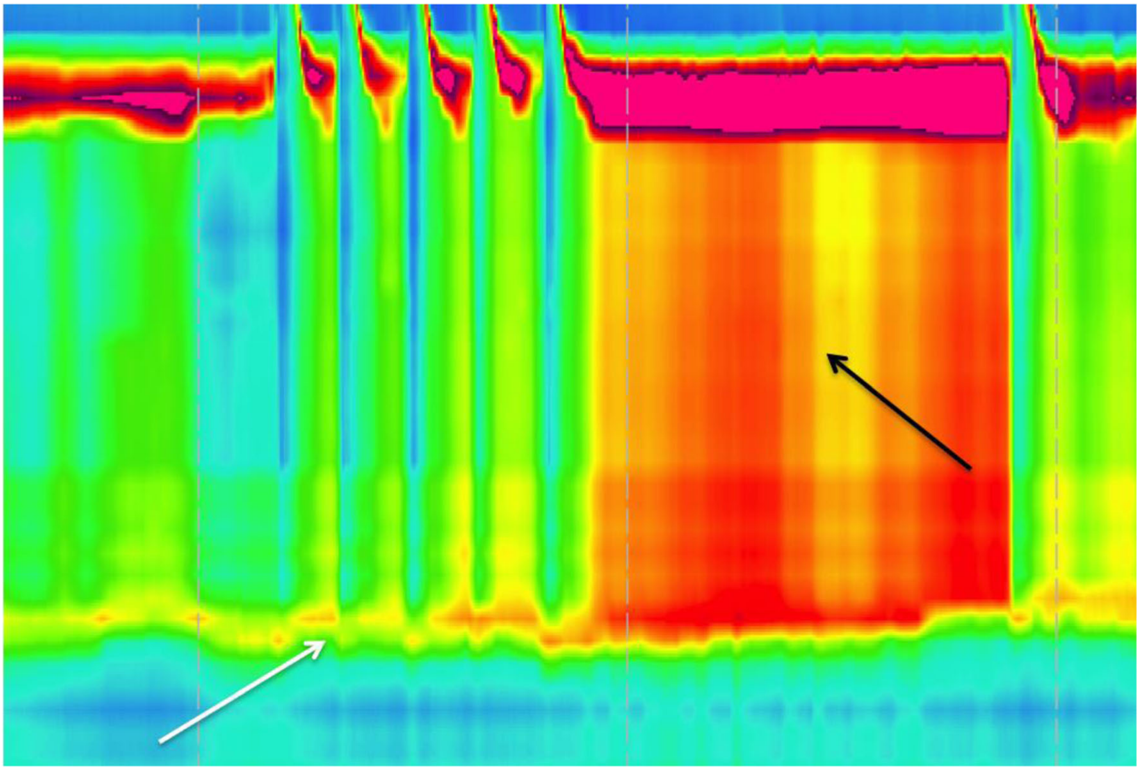

Fig. 5 Achalasia type II—MRS. Fourteen-year-old boy with a 1-year history of recurrent vomiting after meals and dysphagia for solids. His barium swallow had shown intraesophageal reflux, poor esophageal motility, no esophageal dilatation, and a delay in the opening of the gastroesophageal junction but adequate clearance. His endoscopy was macroscopically and histologically normal. A 24-h pH/impedance study excluded GERD. His HRM revealed achalasia type II. Single swallows showed pan-esophageal pressurization and an IRP of 43.7 mmHg (solid-state catheter, Sierra diagnostics). MRS showed pan-esophageal pressurization (*black arrow*) and lack of LES inhibition (*white arrow*)

function. Thus, new parameters such as panesophageal pressurization during single or multiple swallows (Fig. 6) and the lack of sphincter relaxation during multiple rapid swallowing or a 200 ml test could guide diagnosis more precisely.

Abnormal esophageal motor dysfunction is encountered in 41 % of adult and pediatric patients with eosinophilic esophagitis (EoE) with IEM being the most common abnormality noted [104]. Interestingly, IEM is accompanied with early pan-esophageal pressurization and compartmentalized distal pressurization during single swallows with 5, 10, or 20 ml in more than a third of EoE patients [105] while high amplitude contractions and increased number of isolated contractions have been demonstrated in pediatric ambulatory prolonged esophageal manometry [106•]. This provides an example as to how the protocol for performing HRM may need to be adjusted based on the clinical question posed and, more importantly, that the study interpretation should aim to describe firstly the abnormal findings and then classify the pathology according to the CC criteria if appropriate.

HRM and Impedance in Pediatrics

Dysphagia in children can be studied by combining HRM with impedance [107•]. The pressure flow index (PFI) may be used as a complementary marker to the CC criteria in order to clarify whether the reported symptoms are related to defective bolus transit (i.e., poor bolus clearance or high intrabolus pressure in relation to bolus flow).

The diagnosis of rumination syndrome in children is often delayed, on average by 2 years [108], with symptoms often attributed to GERD, intermittent malrotation, cyclic vomiting, and anorexia nervosa. The use of combined esophageal manometry and impedance can help clinicians clinch the diagnosis with the demonstration of a sharp increase in intragastric pressure, also known as the "R-wave," before gastric contents are propelled into the esophagus, which leads to a retrograde drop in impedance [109]. A swallow usually follows each episode of rumination (Fig. 7). In our experience, children with suspected rumination syndrome could benefit from this method, as prompt diagnosis will allow early intervention with behavioral therapy and rehabilitation.

Use of HRM Post-operatively in Pediatrics

As in adults, children who undergo Nissen fundoplication may experience post-operative dysphagia. Investigating these children with esophageal manometry can be very elucidative. Esophageal body abnormalities [110] and esophago-gastric

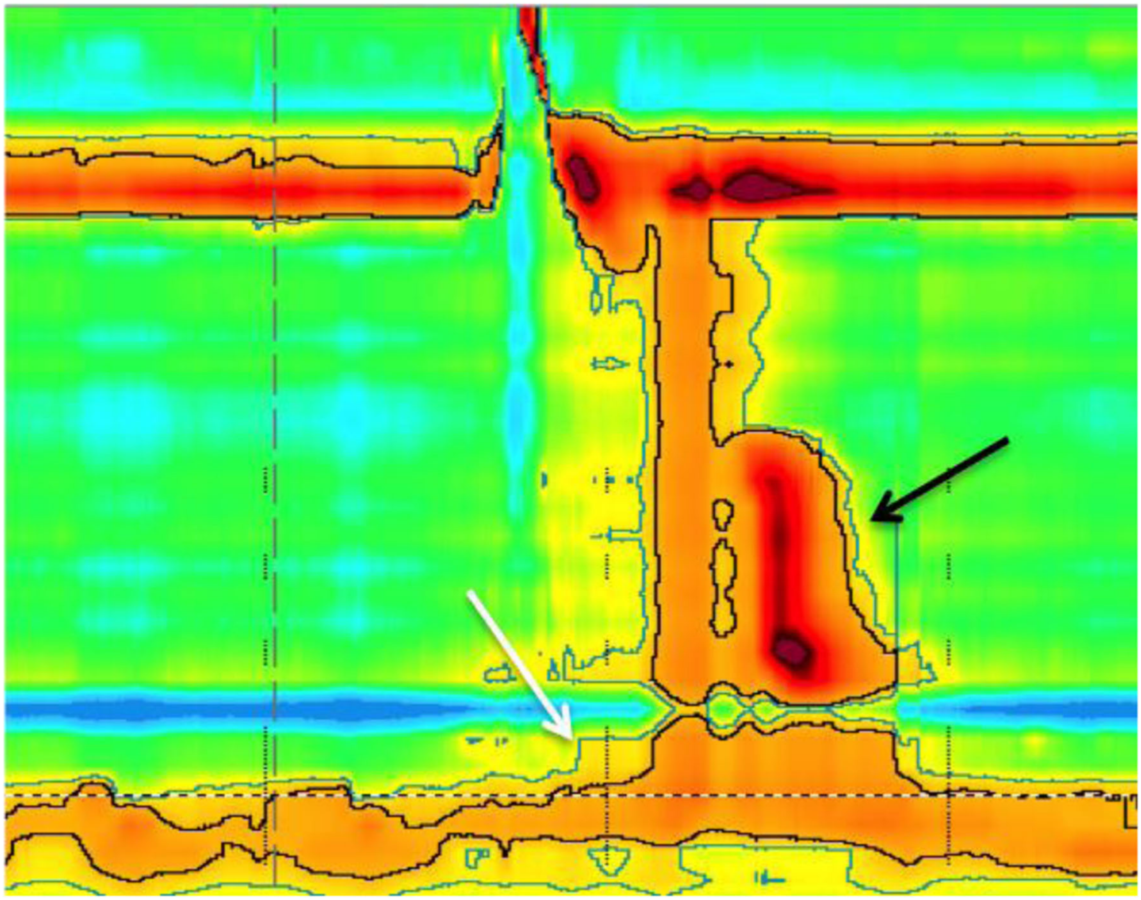

Fig. 6 Achalasia type III. Fifteen-year-old boy who was treated for achalasia with balloon dilatations but showed poor, short-lived response with recurrence of dysphagia for solids. He was considered for a Heller myotomy, and an HRM was performed prior to this (4 months following his fourth balloon dilatation). The HRM showed spastic contractions (*black arrow*) with wet swallows (DL 2.4 s, mean CFV 17 cm/sec, mean DCI 1179 mmHg s cm) and an IRP of 29 mmHg (*white arrow*) (solid-state catheter, Sandhill diagnostics). The MRS and 200 ml water test similarly showed spastic contractions and lack of LES inhibition

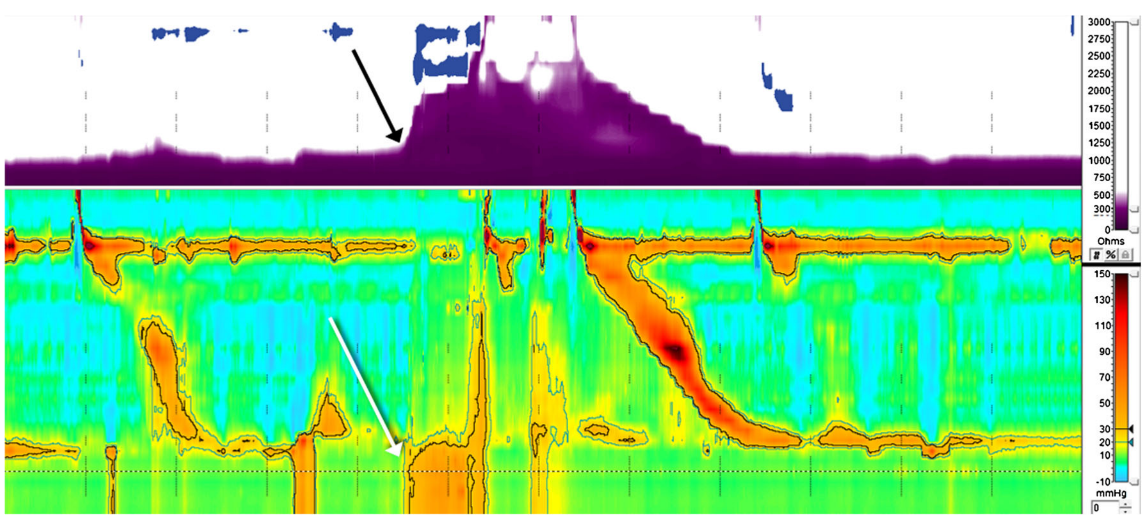

Fig. 7 Rumination (type I). Twelve-year-old boy with a 4-year history of vomiting intermittently and migraines. He was previously diagnosed with cyclic vomiting and had various investigations including neurological and psychological assessments. His HRM study was combined with impedance and a test meal, and an observation period was undertaken at the end of the ten liquid swallows. The esophageal motility was normal, and there were three discrete episodes of increased intra-abdominal pressure (*white arrow*) followed by retrograde liquid flow (*black arrow*) into the esophagus. Each episode was followed by a swallow, which led to clearance of esophageal fluid content

junction obstruction due to a tight wrap may be detected [50] (Fig. 8). In terms of predicting post-operative dysphagia, the combination of esophageal impedance with manometry has been most promising [111, 112]. Lastly, there may also be a role of esophageal manometry for children with congenital structural abnormalities following surgery such as for esophageal atresia [113].

Conclusions

The Chicago Classification offers an internationally accepted systematic approach to diagnosis of esophageal motility disorders. As our knowledge expands and HRM becomes more widely available, we should be aiming to develop the descriptive metrics and parameters of the study and adjust the diagnostic pathways described by the CC. Inclusion of metrics for the EGJ contractile efficacy, esophageal body contractility and peristaltic reserve, and UES parameters will transform the CC into a global assessment algorithm of esophageal disorders. The CC algorithm could be further enhanced by providing evidence-based guidance on complementary HRM diagnostics. This would increase diagnostic yield beyond that obtained by the current standard 10 liquid swallow HRM protocol. Depending on clinical scenario, the clinician should be able to adapt the HRM protocol to include the appropriate provocative test and follow-up with nonmanometric tests as required.

In children, the metrics used should be adjusted for esophageal length and other corroborative HRM findings need to be considered for diagnosis, apart from the currently used CC parameters. The combination of manometry and impedance provides added information on bolus clearance and flow. Outcome studies are needed in order to take the field forward and determine therapy choices and management.

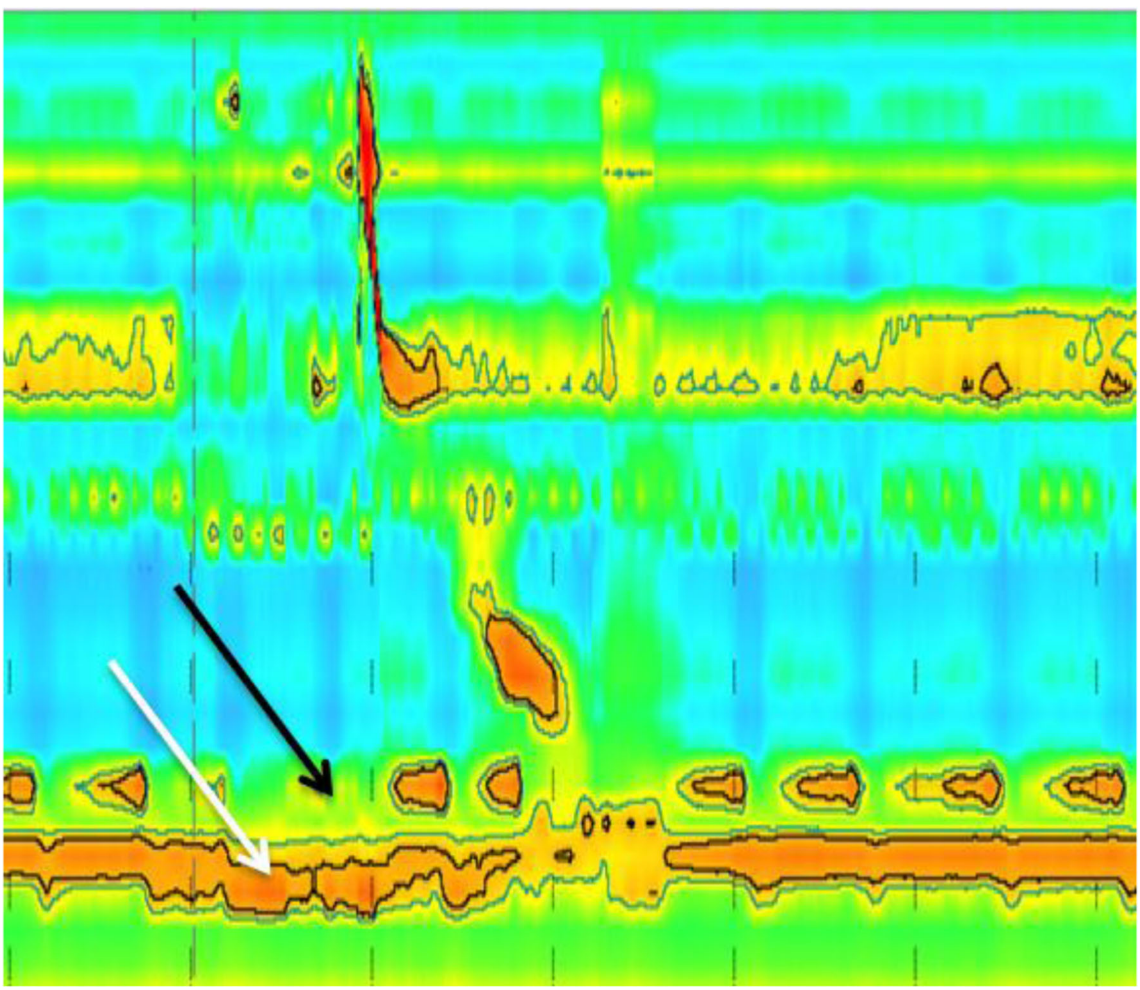

Fig. 8 Post-Nissen. Twelve-year-old girl with Rubinstein-Taybi syndrome who presented with recent onset of dysphagia. She had undergone a Nissen fundoplication at the age of 2 years for poor weight gain and clinically suspected GERD due to ongoing vomiting. Her manometry showed a separated post-ARS EGJ complex (LES and crura: *black arrow*; fundic wrap: *white arrow*). There was relaxation of the LES but lack of relaxation at the level of the fundic wrap. This indicated a tight wrap below the LES level and surgical revision was required

Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were in compliance with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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