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Role of High-Resolution Manometry in Diagnosing Esophageal Motility Disorders - A Literature Review in Line with Chicago Classification V4.0

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ABSTRACT

The Chicago classification is a dynamic evolutionary process that is widely accepted and intended to improve the diagnosis and management of esophageal motility disorders by using high-resolution manometry (HRM). In recent times, Chicago classification version 4 (CCv4.0) was published after two years of work (from November 2018 to October 2020) by the international expert high-resolution manometry group. However, CCv4.0 continued upon the previous hierarchical Chicago classification scheme; CCv4.0 has made several changes to reduce the overdiagnosis of inconclusive patterns in HRM and inappropriate intervention. These changes include: (1) the inclusion of standardized HRM protocol between centers to increase reliability and facilitate research cooperation. This protocol comprises single wet swallows in supine and upright positions and provocation tests (2) Having a conclusive actionable diagnosis of esophageal motility disorder requires both manometric and non-manometric assessment (3) Require a supportive history (dysphagia and/or non-cardiac chest pain) and the manometric pattern of EGJOO, distal esophageal spasm, and hypercontractile esophagus to consider clinically relevant (4) Stringent the diagnostic criteria of ineffective esophageal motility disorder and incorporate fragmented peristalsis into the IEM definition. (5) Provide the metrics of the esophagogastric junction (EGJ) and no longer distinguish between major and minor disorders. Further, Chicago classification version 4 separates EGJ outflow disorder from peristalsis disorders. This literature review aimed to update the literature on esophageal motility disorders in accordance with Chicago classification version 4 (CCv4.0).

Keywords: Chicago Classification v4.0; Esophageal Motility Disorder (EMDs); Esophagogastric Junction Obstruction (EGJOO); Achalasia; Distal Esophageal Spasm (DES); hypercontractile Esophagus (HE); Ineffective Esophageal Motility (IEM); Absent Contractility; High-Resolution Manometry

Abbreviations: CD: Crural Diaphragm; EGJOO: Esophagogastric Junction Outflow Obstruction; MRS: Multiple Rapid Swallows; RDC: Rapid Drink Challenge; DL: Distal Latency; LES: Lower Esophageal Sphincter; IRP: Integrated Relaxation Pressure; DCI: Distal Contractile Interval; IEM: Ineffective Esophageal Motility; EGJ: Esophagogastric Junction; EMDs: Esophageal Motility Disorders

Introduction

The human esophagus is divided into the cervical esophagus, composed of striated muscles, and the thoracic esophagus, made of smooth muscles. Its main function is to transfer swallowed food from the throat to the gut through coordinated contractions known as peristalsis [1]. Disruption of this process can lead to esophageal motility disorders (EMDs), also considered functional disorders affecting the esophageal body, or sphincters due to neuromuscular dysfunction in smooth muscle [2]. EMDs can have a wide range of presentations, from asymptomatic to difficulty swallowing, non-cardiac chest pain, or heart pain [3]. In severe cases, they may lead to aspiration, regurgitation, respiratory problems, and weight loss [4]. EMDs can occur as primary disorders or as part of systemic or secondary diseases, such as systemic sclerosis, diabetes mellitus, Chagas disease, viral infections, and malignancies [2,3]. Despite being rare and having an elusive cause, EMDs significantly impact individuals› quality of life and society. Factors like genetics and environmental factors have been evaluated as potential reasons. Some studies have shown that esophageal motility may correlate with the patient›s age [5]. The diagnosis of EMDs is challenging, requiring a combination of tests like high-resolution manometry (HRM), endoscopy, and barium swallow imaging to support the diagnosis. Advancements in manometry sensor technology and data display have improved the accuracy of EMD diagnosis [2]. HRM, with its higher spatial resolution and more sensors (36 sensors, one cm apart) covering all segments of the esophagus, including sphincters, pharynx, and stomach, has become the standard gold test for diagnosing, classifying, and managing EMDs [6,7]. The data collected is transformed into a dynamic color-coded esophageal pressure topography (EPT) using advanced software algorithms.

The Chicago classification, developed in 2007 by Ray E. Clouse, is an evolving hierarchical system that continues to be refined. The latest version, CCv4.0, was published in 2020 after two years of work by 52 international HRM experts from 20 countries. It includes updates and recommendations for a solid-state HRM catheter with less than 2 cm sensor spacing and a combined impedance catheter [8,9]. CCv4.0 encompasses seven subgroups, covering various aspects such as standard HRM protocol, achalasia, esophagogastric junction outflow obstruction (EGJOO), distal esophageal spasm (DES), hypercontractile esophagus, ineffective esophageal motility (IEM), and esophagogastric junction (EGJ) metrics [10]. These modifications make CCv4.0 more rigorous and accurate compared to the previous CCv3.0. This review aims to determine the role of HRM in diagnosing EMDs in line with CCv4.0 and to find the difference between CCv3.0 and CCv4.0.

Methodology

Search Strategy

The authors conducted a thorough literature review to update the role of HRM in CCv4.0 & the classification of EMDs. They searched multiple databases, including PubMed, ResearchGate, the Cochrane Library, and Google Scholar, using specific keywords related to CCv4.0 and EMDs. Only full-text articles were included, while unpublished data and grey literature were excluded.

Study Screening and Selection

The author conducted a comprehensive literature search and identified a total of 71 citations. After removing duplicates and screening abstracts and titles, 46 articles remained. Four articles were not accessible in full text and were excluded. Thus, 42 articles were considered potentially relevant and reviewed in full. Ultimately, ten articles were included in this study. The research was approved by the Faculty of Life Science and Education, University of South Wales Ethics Subgroup, and Faculty Research Ethics Committee. Details of the excluded articles can be found in Appendix Table 1.

Appendix Table 1.

Articles	First author	Cause of exclusion
Chicago Classification of esophageal motility disorders: Past, present, and future	K. Delay, R. Yadlapati, and Pandolfino	The full article not available free online.
Impact of patient position on esophageal motility disorders using HMRI supine versus upright swallows	Samuel Tanner et al	. The full article not available free online.
Ineffective esophageal motility in CC4.0 better predicts abnormal acid exposure	Qian -Jun Zhuang	aimed to investigate IEM in CC0.4 in context with GERD)
A Short History of High-Resolution Esophageal Manometry	C. Prakash Gyawali, Peter J Kahirlas	The full article not available free online
Effect of breathing training and DNS on lower esophageal sphincter and back pain in patients with gastroesophageal reflux disease	Jandáková, Vladana	focused on lower esophageal sphincter and low back pain in patients with gastroesophageal reflux disease (GERD)
Minimally invasive surgery: hiatal hernia repair—a narrative review	Lina Hua, Geoffrey P. Kohn	(Study about hiatal hernia and management)
Therapeutic Endoscopy and the Esophagus	Linda Y. Zhang	study about endoscopic management
Preface: Esophageal Manometry and Science and Practice of Esophagology	Shahin Ayazi	study the Science and Practice of Esophagology

Update on Esophageal Motility Disorders acer the Recent Chicago Classification 4.0	Agustina Rodil	not in English language
Determinants of reflux perception in patients with non-erosive reflux disease who have reflux-related symptoms on potassium-competitive acid blocker therapy	Noriyuki Kawami	(Investigated potential determinants of reflux perception in patients with non-erosive reflux disease (NERD) who had reflux-related symptoms on potassium-competitive acid blocker (P-CAB) therapy
Evolution of Esophageal Motility Testing: From Kronecker to Clouse	Andrew D. Grubic	aimed to record the major steps in understanding the mechanical esophageal function from the early report of Kronecker and Meltzer in 1883 to the status of high-resolution manometry (HRM)
Laparoscopic Fundoplication Is Effective Treatment for Patients with Gastroesophageal Reflux and Absent Esophageal Contractility	Steven Tran	(Study determined the long-term postoperative outcomes following fundoplication in patients with absent esophageal contractility versus normal motility
The Brief Esophageal Dysphagia Questionnaire shows better discriminative capacity for clinical and manometric findings than the Eckhardt score	Daniel Cisternas	(Compare the ES with the recently developed Brief (BEDQ) in terms of their correlation and discriminative capacity for clinical and manometric findings
Endo FLIP: a new technology	Albis Hani	Aimed to study Endo FLIP used for diagnosis esophageal motility disorders
The Relevance of Ineffective Esophageal Motility to Surgical Practice	Geoffrey P. Kohn	aimed to study provocation testing to predict postoperative dysphagia and to guide management
Esophageal Dysmotility Is Associated with Disease Severity in Eosinophilic Esophagitis (EOE)	Dustin A Carlson	The study evaluated clinical and physiologic characteristics, including esophageal distensibility, associated with secondary peristalsis in patients with EoE
Is EGJOO a Purely Manometric Diagnosis	Benjamin L	(Study reviewed the various modalities used for diagnosis and assessment of EGJOO as well as the available treatments
An investigation into the effect of nasogastric intubation on markers of autonomic nervous function	Humayra Abdul-Razakq	study explored the prevalence and effect of NG on esophageal motor function
Relationship between dysphagia, lower esophageal sphincter relaxation, and esophagogastric junction distensibility	Anand S. Jain	examined the relationship between the DI and IRP and assessed correlations with dysphagia symptoms in patients with achalasia and (EGJOO)
Making Sense of Non achalasia Esophageal Motor Disorders	Benjamin D Rogors	The full article not available free online
Hard to Swallow Results	S. Saboori	a quality improvement (QI) study assesses improve procedural adherence and interpretation of EM
Heterogeneity of primary and secondary peristalsis in systemic sclerosis: A new model of "scleroderma esophagus	Dustin A Carlson	aimed to assess primary and secondary peristalsis in SSc applying (HRM) and (FLIP)
Functional Luminal Imaging Probe (FLIP) as an Adjunctive Modality in Evaluation of Esophageal Dysmotility	Domenico A Farina, Dustin A Carldon	aimed to assess FLIP as value tool to assess esophageal motility disorders
Esophageal Physiologic Testing of Obese Subjects as a Part of Bariatric Surgery Planning	Benjamin D Rogors	assessed the diagnostic value of routine esophageal physiologic testing prior to bariatric surgery
Association of Achalasia with Active Varicella Zoster Virus Infection of the Esophagus	Rishi D Naik	aimed to investigate the possibility that VZV (enteric zoster) might be linked to achalasia
Classifying Esophageal Motility by FLIP Planimetry: A Study of 722 Subjects with Manometry	Carlson Dustin	aimed to classify esophageal motility with FLIP against HMR and CC4.0
Ineffective Esophageal Motility: Need for Improvement in Diagnostic Criteria	Joan W Chen	discussed the phenotyping of IEM and future improvement in IEM diagnosis
S425 The Esophageal Response to the Alleviation of Distension: A Study Utilizing FLIP Planimetry	Carlson Dustin	aimed to evaluate the response of EGJ distensibility during alleviation of distension with FLIP
S383 Proposed Endoscopic Scoring System for Achalasia: The Delayed Esophageal Clearance in Achalasia (DECA) Score	Eillson	aimed to propose DECA scoring system correlate with disorders associated with delayed esophageal clearance
Validation of Clinically Relevant Thresholds of Esophagogastric Junction Obstruction Using FLIP Planimetry	Dustin A Carlson	aimed to assess FLIP to detect EGJO assigned by HMR and CC4.0

Prediction of Esophageal Retention: A Study Comparing High-Resolution Manometry and Functional Luminal Imaging Probe Planimetry	Carlson Dustin	compare HRM and FLIP in predicting esophageal retention on timed barium esophagogram (TBE)
S483 Esophageal Circular Muscle Thickness with Endoscopic Ultrasound Among Esophageal Motility Disorders	Low	compare LES and esophageal body thickness among patient with achalasia
Deep learning based artificial intelligence model for identifying swallow type in esophageal HMR	Wenjun Kou	aimed to classify swallow type
S372 Patients with Ineffective Esophageal Motility (IEM) on Chicago Classification v4.0 Have Weaker Swallows and Worse Bolus Clearance Than Patients Meeting Only v3.0 Criteria	Chon Christy	The full article not available free online

Assessment of Methodological Quality

Each selected article was assessed based on the method of the study, literature search strategy, data extraction, risk of bias, and all parts of methodological qualities using the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) tool and presented in Appendix Table 2.

Appendix Table 2: Q1: did the research questions and inclusion criteria for the review include the components of PICO?

Q2: did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Q3: did the review authors explain their selection of the study designs for inclusion in the review?

Q4: did the review authors use a comprehensive literature search strategy?

Q5: did the review authors perform study selection in duplicate?

Q6: did the review authors perform data extraction in duplicate?

Q7: did the review authors provide a list of excluded studies and justify the exclusions?

Q8: did the review authors describe the included studies in adequate detail?

Q9: did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Q10: did the review authors report on the sources of funding for the studies included in the review. Q11: if meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?

Q12: if meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Q13: did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

Q14: did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: if they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: did the review authors report any potential sources of conflicts of interest, including any funding they received for conducting the review?

Included study	Fox et al	Yadlapati et al	Khan et al	Yadlapati R, Pandolfino JE, Fox MR, Bredenoord AJ, Kahrilas PJ	Roman et al	W. Chen et al	Gyawali et al	Delay, Krause and Yadlapati	Yadlapati and Kahrilas	Karallas et al
Q1	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q2	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q3	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q4	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q5	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

Q6	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q7	No	No	No	No	No	No	No	No	No	No
Q8	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q9	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q10	No	yes	No	No	No	No	No	No	yes	No
Q11	No	No	No	No	No	No	No	No	No	No
Q12	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q13	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q14	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q15	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Q16	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low

Quality of Evidence

The grading of the recommendation, assessment, development, and evaluation (GRADE) tool was used to assess and evaluate the quality of evidence and risk of bias for CCv4.0 recommendations in the main findings of this review as presented in Appendix Table 3.

Appendix Table 3.

Recommendations	Agreement in %	Strength of agreement	GARDE level of evidence
Type1 achalasia: a conclusive diagnosis defined as an elevation of median IRP and absent contractility (100% failed peristalsis)	98%	Strong	Very low
Type11 achalasia: a conclusive diagnosis defined as an elevation of median IRP and absent contractility (100% failed peristalsis) with 20% or more PEP.	98%	Strong	Very low
Type 111 achalasia: a conclusive diagnosis defined as an elevation of median IRP and absent contractility (100% failed peristalsis) with evidence of spasm (20% or more swallows with premature contraction)	88%	Strong	Very low
An inconclusive diagnosis of type I or II achalasia includes median IRP in the upper limit in primary and secondary positions with absent contractility and no appreciable peristalsis with or without PEP in 20% or more swallows	91%	Strong	Not applicable
In the setting of type1 and II achalasia with appreciable peristalsis with changing position requires supportive test and can shift the diagnosis to an inconclusive.		Accepted clinical observation	Not applicable
Supportive test with a TBE, preferably with tablet, and/or FLIP is required in patients with an inconclusive diagnosis of achalasia and presenting with dysphagia	91%	Strong	Very low
An inconclusive diagnosis of type III achalasia includes an abnormal IRP with evidence of spasm and evidence of peristalsis. If these cases fulfill strict criteria for EGJOO (as detailed in the EGJOO section) these patients should be classified as EGJOO with spastic features, which may represent an achalasia variant		Accepted clinical observation	
The cutoff of spasm in 20% of swallows is arbitrary, and confidence in a diagnosis of a type III achalasia variant may be increased with a higher number of premature/spastic swallows		Accepted clinical observation	
Opioid medication should be stopped before preforming HRM because Opioid associated with type III achalasia	85%	Conditional	Low
HMR finding of EGJOO alone is considered clinically inconclusive		Strong	
Manometric findings indicate EGJOO diagnosis is defined as increased median IRP in supine and upright positions and 20% or more of swallows with increased intrabolus pressure in supine position with evidence of peristalsis		Conditional	Low
Clinically Relevant diagnosis of conclusive diagnosis EGJOO warrants relevant symptoms, HRM finding, and at least one supportive test (TBE is preferred in conjunction with a barium tablets swallow and /or FLIP).		Conditional	Moderate
Clinically relevant symptoms of EGJOO are dysphagia and /or non-cardiac chest pain.		Conditional	Low

An inconclusive diagnosis of EGJOO defined as Isolated increased IRP in primary or secondary positions, isolated increased intrabolus swallow pressure in the supine position.		Conditional	Low
A conclusive manometric diagnosis of DES is defined as presence of at least 20% of premature contractions	86%	Strong	Low
Esophageal contractile activity must be distinguished from other causes of pressure rise in the distal esophagus such as intrabolus pressure and/or artifact.	100%	Strong	Very low
The CDP might be difficult to identify. In this setting, alternative methodologies need to be considered to diagnose DES	86%	Strong	
A clinically relevant diagnosis of DES requires both clinically relevant symptoms and a conclusive manometric diagnosis of DES	84%	Conditional	Low
Clinically relevant symptoms for DES include dysphagia and non-cardiac chest pain		Accepted clinical observation	
The presence of at least 20% of premature contractions (DL < 4.5 s) but with a DCI < 450 mm Hg ·s ·cm is inconclusive for a manometric diagnosis of DES	81%		Low
Hypercontractile esophagus describes a distinct manometric abnormality defined by excessive peristaltic vigor, which may include excessive LES after-contraction, not associated with a mechanical obstruction	84%	Conditional	Very Low
A hypercontractile esophageal contraction is defined as a DCI >8,000 mmHg ·s ·cm	84%	Conditional	Low
A clinically relevant diagnosis of hypercontractile esophagus requires both clinically relevant symptoms and a conclusive manometric diagnosis of hypercontractile esophagus	90%	Strong	Very low
A conclusive manometric diagnosis of hypercontractile esophagus is defined as 20% or more hypercontractile supine swallows	80%	Conditional	Very low
Clinically relevant symptoms of hypercontractile esophagus include dysphagia and noncardiac chest pain	95%	Strong	Very low
A diagnosis of hypercontractile esophagus can only be made when criteria for achalasia or distal esophageal spasm are not met and a mechanical obstruction has been carefully ruled out	98%	Strong	Very low
The diagnostic classification "fragmented peristalsis" should be removed. This concept should be incorporated into the overall diagnosis of IEM	86%		Very low
A swallow with a DCI<450 mmHg.cm.s consistence with ineffective swallow	91%		
A conclusive diagnosis of IEM requires >70% ineffective swallows or ≥50% failed peristalsis	91%		Very low
The presence of 50 to 70% of ineffective swallows is inconclusive for a diagnosis of IEM. Supportive testing will strengthen confidence in IEM diagnosis in these cases	80%		Very low
Supportive testing for IEM could include poor bolus transit on impedance or barium esophagography	80%		Very low
Supportive testing for IEM could include lack of contraction reserve on multiple rapid swallow	80%		Very low
The EGJ complex should be measured during quiet respiration in the baseline recording in a segment relatively devoid of swallowing and/or recording artifacts. This also refers to measurement of intragastric pressure, which should be measured below the CD over three complete respiratory cycles, preferably in the same segment as used to measure the EGJ-CI	95%	Strong	
LES-CD separation should be scored as the distance between the center of the CD and LES signal during inspiration, unless obscured in which case the LES position should be scored at expiration	91%	Strong	
The RIP is the axial location at which the inspiratory change in pressure transitions from an inspiratory increase, characteristic of intraabdominal recordings, to an inspiratory decrease, characteristic of intrathoracic recordings	95%	Strong	Very low
There can be 3 subtypes of EGJ pressure topography (1) No hiatal hernia: LES-CD separation 1 cm and RIP between the LES and CD (3) Hiatal hernia, proximal RIP: LES-CD separation >1 cm and RIP proximal to the LES	80%	Conditional	Low

In the normal state (EGJ subtype 1), the RIP localizes at the proximal margin of the LES-CD (EGJ) complex.	88%	Strong	Low
With hiatus hernia, the RIP can localize either between the LES and CD or proximal to the LES	81%	Conditional	Low
With an LES-CD >3 cm, the RIP location and relation to LES can be unreliable. However, these patients usually have an incompetent EGJ.	81%	Conditional	Low
The EGJ-CI should be referenced to intragastric pressure and expressed in units of mmHg ◦cm	86%	Strong	
Intragastric pressure should be measured during quiet respiration in the baseline recording in a segment relatively devoid of swallowing and/or recording artifacts, preferably the same segment as used to measure the EGJ-CI.	95%	Strong	

Findings of HRM Protocol in the CCv4.0

CCv4.0 introduces significant changes to enhance the HRM protocol, incorporating position changes, and adding provocation tests. Standardizing the HRM protocol in CC4.0 is crucial for improving procedure reliability and consistency, enabling collaborative research among different centers [11]. CCv4.0 records HRM findings in both supine and upright positions, facilitating the diagnosis of various motility conditions. The inclusion of provocative tests in CC4.0 has led to increased sensitivity and specificity of HRM studies.

Patient›s Positions in line with CCV4.0

After HRM catheter insertion through the nostril to the esophagus and stomach, the patient rests for 60 seconds (Adaptation period) and takes three deep inspirations to confirm the catheter›s position. The procedure can begin in either an upright/supine position, with a preference for starting in the supine position according to CCv4.0 protocol recommendations. Clinicians may modify the protocol based on available resources if they adhere to the normative values [11].

Supine Position: Patients start with ten wet swallows, and if the results are inconclusive, they switch to the upright position and perform at least five more swallows. Changing positions helps eliminate conditions specific to the supine position, like false-positive EGJOO identification.

Upright Position: Patients begin with five wet swallows to determine the conditions of the upright position, such as false-positive IEM diagnosis. The upright position affects bolus transportation velocity and the distal contractile interval (DCI) in the esophagus due to the gravity effect.

The CCv4.0 working group suggests obtaining swallows in both positions, particularly if unexpected EMD is found. While single wet swallows in upright and supine positions, together with provocative tests, can be time-consuming, in certain cases, if a conclusive diagnosis of achalasia type I or II is achieved from the primary position, the full protocol can be avoided. Nevertheless, if the CCv4.0 protocol is not fully completed, applying position-appropriate normative values is recommended [11].

HRM Diagnostic Threshold

The CCv4.0 working group determines the cut-off thresholds of HRM metrics when evaluating deglutition relaxation through lower esophageal sphincter (LES)/EGJ with the use of integrated relaxation pressure (IRP). Assess vigorous esophageal body contraction using DCI. The latency of deglutition inhibition by using distal latency (DL) [10]. Table 1 illustrates the HRM metrics and thresholds according to CCv4.0 (the author inspired it from (Yadlapati, et al. [9]).

Table 1: HRM metrics and thresholds according to CCv4.

Evaluation	Pressure tomography metric	Diagnostic threshold	Additional points
Relaxation pressure across the EGJ in response to deglutition	IRP	Abnormal deglutitive IRP relaxation: •Supine median IRP 15mmHg or more (Medtronic) Supine median IRP22 mmHg or more (Laborie/Diversatek) Upright median IRP 12 mmHg or more (Medtronic) Upright median IRP15 mmHg or more (Laborie/Diversatek)	IRP more than 12 mmHg (Medtronic) on rapid drink challenge (RDC) or IRP more than 25 mmHg (Medtronic) on solid test meal supports outflow obstruction

Esophageal peristalsis	DCI contractile vigor Contractile wavefront integrity	Standard l contractile DCI between 450-8000 mmHg.s.cm. Weak contractile DCI of more than 100 and less than 450 mmHg.s.cm. Failed peristalsis DCI less than 100 mmHg.s.cm Hypercontractile swallows more than 8000 mmHg.s.cm. Ineffective swallows: weak contraction or failed peristalsis/ peristalsis break more than 5 cm in the setting of DCI more than 450 mmHg.s.cm.	
Latency deglutitive inhibition	DL	Premature/Spastic contraction: DL<4.5 sec in the setting of DCI more than 450 mmHg.s.cm	
Pressurization	Isobaric contour	Pan esophageal pressurization PEP: isobaric contour 30 or more mmHg. Intrabolus pressurization: Isobaric contour 20 or more mmHg in the supine position (Medtronic)	PEP more than 20 mmHg on RDC or solid test meal support outflow obstruction.

Additional HRM Maneuvers

The CCv4.0 working group recommends incorporating provocation tests in the HRM protocol to assess esophageal motility. This is essential because a limited number of wet swallows during supine or upright positions may not always be sufficient, especially in symptomatic patients [11]. These additional maneuvers include multiple rapid swallows (MRS), rapid drink challenge (RDC), ingestion of more viscous material, single solid swallows, and test meals (using either the patient›s food or pre-prepared meals). The CCv4.0 working group has reached a consensus on how to analyze, interpret, and report the results of these provocation tests [10]. Figure 1 demonstrates using of provocation tests during CCv4.0 protocol in supine and upright positions (the author inspired it from Fox, et al. [11]).

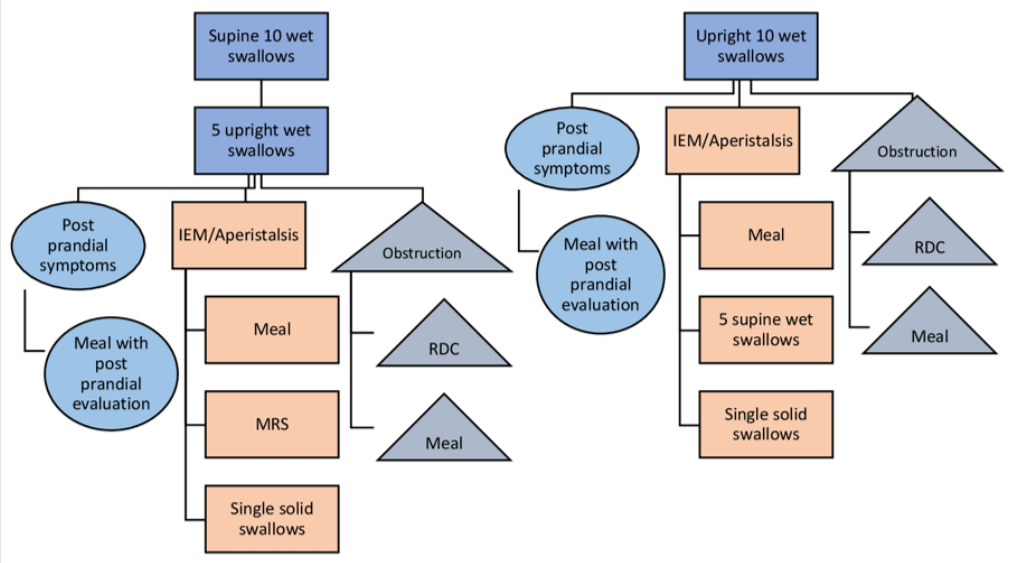

Figure 1: Guidance to apply provocation test in the CCv4.

Multiple Rapid Swallows (MRS): The CCv4.0 working group recommends the use of a syringe to deliver 2 ml of fluid, repeated five times with 2-3-second intervals, as part of the MRS maneuver. This maneuver is performed in the supine position and may be repeated up to three times to confirm the presence of peristalsis reserve, as post-contraction augmentation varies. However, MRS lacks normative values and specific diagnostic criteria, requiring further research. The expected response during MRS is the absence of esophageal contraction (DCI < 100 mm Hg.s.cm) with complete deglutition inhibition of the LES, along with post-MRS contraction augmentation. This response would suggest the presence of peristalsis reserve, especially if a diagnosis of IEM is made during single wet swallows [11].

Rapid Drink Challenge (RDC): The CCv4.0 working group recommends performing RDC in an upright position minimizing the risk of aspiration. The RDC involves swallowing 100-200 ml of water (preferably 200 ml) with a straw. During RDC, assess the contraction inhibition of the esophageal body (DCI) & IRP. The expected response is a DCI < 100 mm Hg.s.cm, total inhibition of the lower esophageal sphincter, with no evidence of significant motility disorders post-RDC [10]. RDC is a common and easy-to-perform additional provocation test that increases the sensitivity of HRM. Studies have established normative values with a sensitivity of 80% and specificity of 93%. Furthermore, patients with moderate HRM throughout single wet swallows can receive a conclusive diagnosis by performing the RDC maneuver [11].

Three patterns can be detected during RDC:

- Hyperparasite pattern (standard).
- A brief hyperparasite pattern (weakness of deglutition inhibition) occurs in the non-obstructive hypercontractility.
- prolonged hyperparasite pattern (Impairment of IRP).

Single Solid Swallow Maneuvers: Including single solid swallows in the HRM protocol improves the diagnosis of EMDs, especially EGJOO. Studies reveal that single swallows increase DL & DCI while reducing significant breaks in the contractile front [10]. The CCv4.0 working group suggests swallowing a 1-2 cm cube of soft biscuit, buttered bread, cake, or dumpling, after chewing it. At least five (preferably 10 swallows) during HRM protocol are recommended, and the esophageal pressure is measured using Medtronic software. The diagnostic cut points for EGJ disorder are IRP > 25 mm Hg and DL > 4.5 seconds (indicating effective contraction) with fewer than a small break in the contractile front (<3 cm) & DCI > 1000 mmHg.cm. s (vigorous contraction). If a minimum of 20% of single swallows lead to effective contractions, it indicates EGJOO; otherwise, it suggests IEM for solid swallows [11].

Solid Test Meal: CCv4.0 recommends this test for patients with esophageal symptoms when other maneuvers are inconclusive or fail to identify the underlying cause. It can also help detect peristalsis reserve in patients suspected of having IEM during water swallows [12]. CCv4.0 recommends patients undergo a standard test meal (200 g) in 8 minutes, producing 20-30 pharyngeal swallows and abnormal EGJ function is considered when having two or more swallows with IRP>25 mm Hg (in the Medtronic system). The addition of the test meal has increased the diagnostic yield to nearly 50% for EGJOO, and HRM with meal test shows higher sensitivity (85%) compared to single water test (54%) and barium esophagogram. The HRM protocol with solid meal test and impedance can be extended to post-prandial periods for identifying other functional disorders, for example, rumination syndrome, volume reflux, and supra-gastric belching [11].

Findings of EMD Classification in the CCv4.0

CCv4.0 classifies EMDs based on peristalsis and EGJOO, building on CCv3.0 (Figures 2A & 2B). However, CCv4.0 extends the diagnosis beyond HRM findings, incorporating additional tests (Provocation tests, timed barium esophagogram, and FLIP) and considering clinical relevance to support HRM findings [13]. CCv4.0 has updated all EMDs, requiring additional tests and a history of obstructive symptoms for a definitive diagnosis of EGJOO. The IEM definition is now more precise, including fragmented peristalsis. However, treatment progress for achalasia and absent contractility remains limited. DES and hypercontractile esophagus diagnoses remain unchanged due to insufficient data. The categorization of major and minor disorders has been eliminated as minor disorders like IEM are now considered major disorders under the new definition [12]. The differences between the diagnosis of EMDs by CCv4.0 and CCv3.0 are summarized in Table 2.

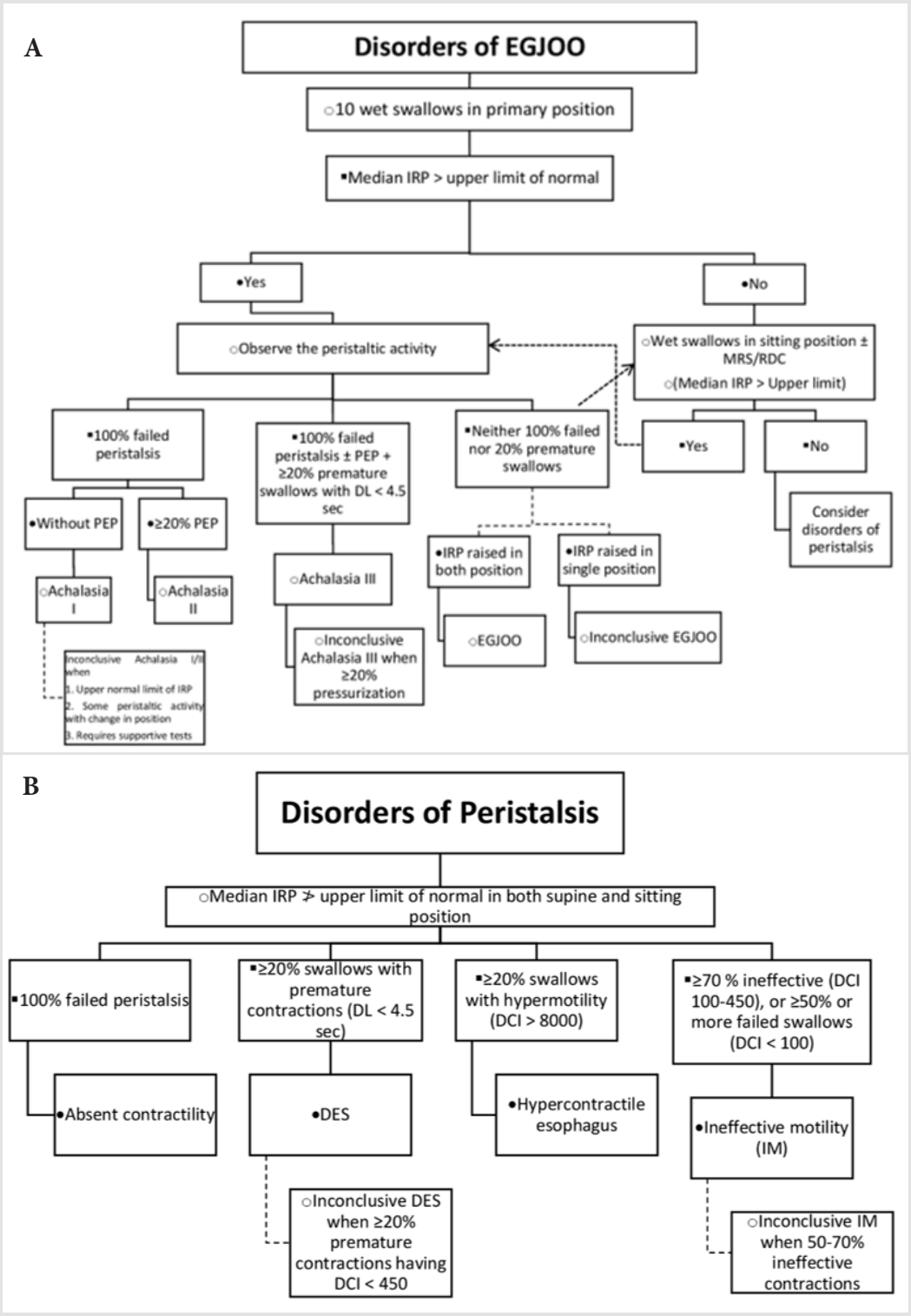

Figure 2:

A. CCv4.0 classification scheme for EGJOO disorders.

B. CCv4.0 classification scheme for Peristaltic disorders.

Table 2: The difference between CCv4.0 and CCv3.0.

Diagnosis	CCv3.0	CCv4.0
Type I achalasia	Median IRP increased, absent peristalsis 100%.	Median IRP increased in supine/or upright position, absent peristalsis 100%.
Type II achalasia	Median IRP increased, absent peristalsis 100%, plus 20% or more PEP.	Median IRP increased in supine/or upright position, absent peristalsis 100% +20% or more PEP.
Type III achalasia	Median IRP increased, failed peristalsis 100%, plus 20% or more swallow with spasm	Median IRP increased in supine/or upright position, failed peristalsis 100%, plus 20% or more swallow with spasm
EGJOO	Median IRP increased but not meet the criteria of achalasia type I-III	Median IRP increased in both supine and upright positions + Normal peristalsis + elevated supine intrabolus pressure + symptoms (dysphagia-noncardiac chest pain) + at least one confirmatory non-HRM supportive test.
Absent contractility	Normal median IRP, absent peristalsis 100%	Normal median IRP, absent peristalsis 100%
Distal esophageal spasm	Normal median IRP+ 20 % or more swallow spasm	Normal median IRP+ 20 % or more swallow spasm+ obstructive symptom (dysphagia – non-cardiac chest pain)
Hypercontractile esophagus	Normal median IRP+ 20 % or hypercontractile esophagus	Normal median IRP+ 20 % or more hypercontractile esophagus+ obstructive symptom (dysphagia – non-cardiac chest pain)
Ineffective esophageal spasm	50% or more ineffective swallows.	70 % ineffective and/or fragmented, or 50% or more failed swallow.

Esophagogastric Junction Outflow Obstruction (EGJOO) Disorders: The CCv4.0 working group has divided EGJOO disorders into achalasia (type I, II, III) and EGJOO with the recommended criteria of abnormal IRP in the first position [12].

Achalasia: The subclassification of achalasia in CCv4.0 remains unchanged as was in the previous classification. CCv4.0 defined achalasia as abnormal median IRP in 10 wet swallows during primary position (upright or supine) and 100% absent peristalsis. The definition of Absent peristalsis is either no peristalsis at all or premature contractility with DL < 4.5 sec. Pan esophageal pressurization (PEP) can differentiate between type I and II achalasia. CCv4.0 refined the definition of type III achalasia from the previous CCv3.0 [14].

Conclusive Diagnoses of Achalasia and Subtypes: Although HRM protocol in Chicago classification version 4 consists of primary and secondary positions for wet swallows, a conclusive diagnosis of achalasia requires a primary position only [14].

Type I Achalasia (Classic): CCv4.0 defines type I achalasia as a late stage of the disease, with median IRP raised above the upper limit of normal and 100% absent peristalsis (Figure 3A) [14].

The most common subtype is the same as in the previous Chicago classification (Figure 3B). CCv4.0 defines it with an abnormal median IRP compared to the upper limit of normal, 100% absent peristalsis, & 20% or more of swallows showing pan esophageal pressurization [12].

Type III Achalasia: It is considered a rare subtype whose definition has been changed by the CCv4.0 working group [14]. CCv4.0 defined type III achalasia as an elevated median IRP compared to the upper limit of normal with 20% or more swallows showing premature contractions (DL < 4.5 seconds and DCI ≥ 450 mmHg.s.cm) and no evidence of peristalsis [12]. However, the cutoff of 20% swallows with premature contractions is considered arbitrary, and higher numbers of premature spasms may increase confidence in diagnosing type III achalasia (Figure 3C). It is worth noting that chronic daily use of opioids has been associated with premature contractions, so CCv4.0 recommends discontinuing opioids before HRM study if possible [14].

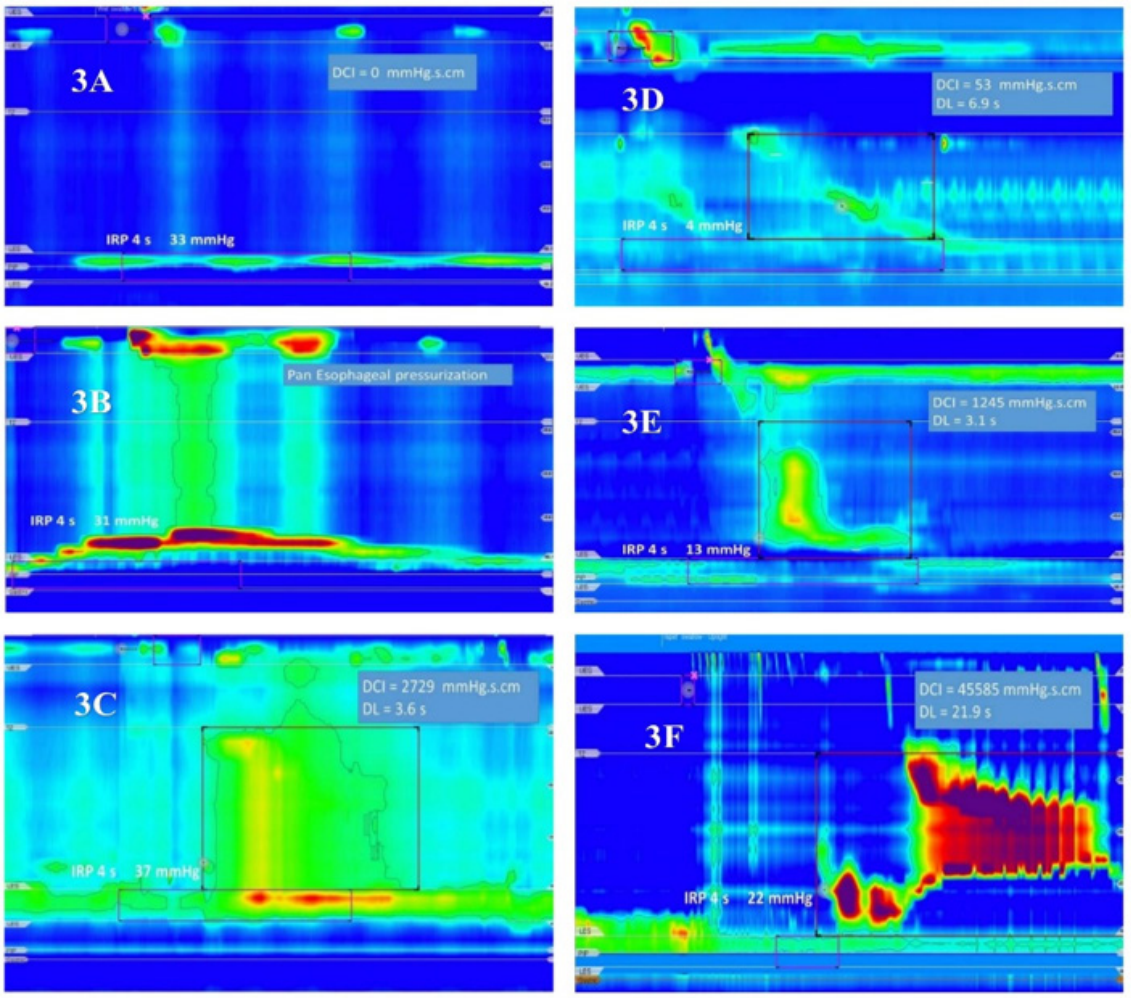

Figure 3:

A. Is representative of type I achalasia: Elevated integrated relaxation pressure (IRP) with failed peristalsis (DCI<100 mmHg.s.cm) and no pan esophageal pressure (PEP).

B. Represents type II achalasia: elevated IRP with failed peristalsis (DCI<100 mmHg.s.cm) and PEP.

C. represents type III achalasia, elevated IRP with a normal DCI, and evidence of spasm (distal latency (DL) is 3.6 Seconds).

D. Is a representation of absent contractility with 100% failed peristalsis but normal integrated relaxation pressure (IRP).

E. Represents DES with > 20% premature contraction (distal latency DL less than 4.5) and DCI more than 450mmHg.s.cm and normal IRP.

F. Is a representation of hypercontractile esophagus.

Inconclusive Diagnosis of Achalasia

CCv4.0 classified type me and II achalasia as inconclusive diagnoses if median IRP in both the primary and the secondary positions fell within the upper limit of normal, in addition to failed peristalsis in less than 20% of swallows. This is regardless of signs of pan esophageal pressurization. Additionally, an inconclusive diagnosis can be made if there is evidence of peristalsis with changing position in type I or type II achalasia in the primary position, requiring a supportive test (accepted clinical observation). For type III, an inconclusive diagnosis is made if there is an abnormal median IRP and premature contractions with evidence of peristalsis. If the patient fulfills the criteria of EGJOO, the diagnosis of EGJOO with spasms can be considered [14].

Esophagogastric Junction Outflow Obstruction (EGJOO)

Approximately 10% of HRM patients exhibit EGJOO motility disorder, making HRM the gold standard for diagnosing EMDs. However, around 30% of these cases may not require clinical action, leading to potentially inappropriate treatments due to factors like opioids, benign mechanical obstruction, or artifacts [10]. To enhance the specificity and reduce over-diagnosis of EGJOO, CCv4.0 reviewed

previous literature and identified different overlapping patterns of peristalsis, including EGJOO with IM, EGJOO with spasm, EGJOO with hypercontractility, and EGJOO with intact peristalsis. Thus CCv4.0 working group has made a more stringent criterion for the diagnosis of EGJOO that requires all the following [12]:

- Raised IRP in both supine and upright positions.
- 20% or more of supine swallows should have elevated intrabolus pressure.
- The presence of clinical symptoms including dysphagia and/or non-cardiac chest pain.
- TBE and FLIP, two tests that are not supportive of HRM, show signs of outflow obstruction.

The CCv4.0 working group provides these recommendations to reach a «clinically relevant conclusive diagnosis» of EGJOO as summarized in Table 3.

Table 3: CCv4.0 update on esophageal motility disorders.

Diagnosis	Update in CCv4.0
EGJOO disorders	
Type I achalasia	Elevated median IRP in supine/or upright position + 100% failed peristalsis,
Type II achalasia	Elevated median IRP in supine/or upright position +100% failed peristalsis+≥ 20% PEP.
Type III achalasia	Elevated median IRP in supine/or upright position +100% failed peristalsis+≥ 20% swallows with DES.
Conclusive EGJOO	Elevated median IRP in supine and upright position + elevated supine intrabolus pressure + symptoms (dysphagia-noncardiac chest pain) + at least one confirmatory non-HRM supportive test
Inconclusive EGJOO	Elevated median IRP in supine or upright position + elevated supine intrabolus pressure + symptoms (dysphagia-noncardiac chest pain) + at least one confirmatory non-HRM supportive test
Peristaltic disorders	
Absent contractility	Normal median IRP, absent peristalsis 100%
Distal esophageal spasm	Normal median IRP+ ≥20 % swallow spasm+ obstructive symptom (dysphagia – non-cardiac chest pain)
Hypercontractile esophagus	Normal median IRP+ ≥20 % hypercontractile esophagus+ obstructive symptom (dysphagia – non-cardiac chest pain)
Ineffective esophageal motility	>70 % ineffective and/or fragmented, or 50% or more failed swallow.

Inconclusive Diagnosis of EGJOO

The CCv4.0 working group defined the inconclusive diagnosis of EGJOO [10] as an isolated increase in IRP in primary or secondary positions or an isolated increase in intrabolus pressures during the supine position (Low GRADE, Conditional recommendation).

Additional points for EGJOO

The CCv4.0 working group considers the following points quite supportive but not necessary for the diagnosis of EGJOO [10]:

- Evidence of outflow obstruction and esophageal pressurization during RDC.
- If the patient›s symptoms are temporally related to an outflow obstruction through a solid test meal, this information is important.
- Abnormal EGJ function after pharmacological provocation.

Disorder of Peristalsis

Disorders of peristalsis disorders in the CCv4.0 scheme remain the same as in CCv3.0. including DES, absent contractility, IEM, and hypercontractile esophagus [13]. Furthermore, fragmented peristalsis is still not considered a separate disorder but rather a diagnostic component of IEM. The definition of Peristaltic disorders requires a normal median IRP with the exclusion of conclusive EGJOO [10].

Absent Contractility

The diagnosis of absent contractility remains unchanged according to CCv3.0. It is defined as a normal median IRP on the primary and secondary sides, together with 100% failed peristalsis (DCI <100 mmHg.s.cm) (shown in Figure 3D). An inconclusive diagnosis of absent contractility is considered when the median IRP falls within the upper limit, especially in the supine position between 10 mmHg to 15 mmHg (Medtronic system), in symptomatic patients with dysphagia. This requires excluding type I achalasia through provocation tests and supportive tests [10]. Absent contractility is idiopathic and has a prevalence of 0.4% in 469 healthy volunteers and 3.2% in 1081 patients assessed for anti-reflux surgery [15]. It can also be seen in patients having mixed connective tissue diseases and gastroesophageal reflux diseases [16].

Distal Esophageal Spasm (DES)

The CCv4.0 working group recommends considering together HRM findings and clinical presentation to define clinically relevant DES (Figure 3E). The definition of conclusive DES requires consideration of the following points [17]:

- At least 20% of premature contraction (DL less than 4.5 seconds)
- DCI more than 450mmHg.s.cm.
- Presence of dysphagia and/ or non-cardiac chest pain.
- Normal EGJ relaxation.

The finding of DES can be challenging due to difficulties in localizing contractile deceleration points (CDP). CCv4.0 recommends considering various techniques for diagnosing DES and distinguishing intrabolus pressure from esophageal contraction artifacts. Although DES is a concern, there is insufficient evidence to support these concerns [17]. Inconclusive DES is defined as having at least 20% of premature contractions with DL > 4.5 seconds & DCI < 450 mm Hg.s.cm. Supportive tests like barium esophagogram, FLIP, and MRS during HRM can aid in confirming the diagnosis. It is important to distinguish primary DES from secondary DES, where type III achalasia and factors like opioid use or GERD may contribute to secondary DES [16].

Hypercontractile Esophagus (HE)

The CCv4.0 working group suggests using manometric findings and relevant symptoms (non-cardiac chest pain and/or dysphagia) for diagnosing clinically relevant HE [10]. The manometric findings for a conclusive diagnosis remain unchanged from CCv3.0, which includes 20% or more hypercontractile supine swallows with DCI >8000 mmHg.s.cm with normal IRP (Figure 3F). Before making the HE diagnosis, the CCv4.0 working group suggests excluding distal esophageal obstruction or achalasia, as HE can be associated with other abnormalities like GERD and EGJOO. The introduction of three manometric subtypes (single peaked, multipeaked/Jackhammer, vigor LES after contraction) of HE is not recommended by the CCv4.0 working group. The following statements did not meet the criteria of agreement in CCv4.0 as they were unable to meet 85% agreement [18]:

- HE should be retained as a major condition of peristalsis and not as a minor one (65%appropriate).
- HRM should be annexed with an impedance study for the best possible detection of intrabolus pressure, flow time, and bolus clearance via esophagus and EGJ (67% appropriate).
- The hypercontractile esophagus is not synonymous with the Jackhammer esophagus and should be considered a subtype of HE (76%appropriate).
- The diagnosis of HE should be supported by the manometric findings of the elevated intrabolus pressure (60% appropriate)
- The diagnosis of HE should be supported by an abnormal RDC test (53% appropriate).
- HRM diagnosis of HE should be supported by the absence of contraction reserve on MRS (56% appropriate).
- Response to medications (nitrate, calcium channel blockers, phosphodiesterase inhibitors, etc.) should be considered as a support to HE diagnosis (51% appropriate).

Ineffective Esophageal Motility (IEM)

The CCv4.0 working group modified the previous CCv3.0 classification of the esophageal hypomotility disorder into two groups in the context of normal LES relaxation.

- Absent peristalsis
- Ineffective motility disorder

The CCv4.0 working group included fragmented peristalsis as part of the Ineffective Esophageal Motility (IEM) definition [10]. The criteria for a conclusive IEM diagnosis were refined, requiring more than 70% ineffective swallows or at least 50% failed peristalsis. These ineffective swallows are defined by a DCI of 100 to 450 mmHg.s.cm or more than 5 cm transition zone fragmentation in peristalsis, while failed peristalsis is defined as a DCI of less than 100 mmHg.s.cm. Patients with ineffective swallows between 50-70% are given an inconclusive IEM diagnosis, and the CCv4.0 working group recommends additional supportive tests like barium esophagogram or HRM with impedance to strengthen the IEM diagnosis, particularly by showing poor bolus transit during MRS and lack of contraction reserve [15]. To sum up the disorders of peristalsis by CCv4.0, Table 3 gives a complete picture in this regard.

Esophagogastric Junction Barrier Metrics

The CCv.4.0 working group guides understanding EGJ metrics, anatomy, integrity, and contractile vigor during baseline position, which was lacking in the previous Chicago classification [10]. The EGJ is a complex sphincter composed of the crural diaphragm (CD) and LES with different physiological control processes and pathophysiology. The working group identified four changes with EGJ assessment, including EGJ contractile integral (EGJ-CI), LES-CD separation, intragastric pressure, and respiratory inversion point (RIP). CCv4.0 stated the following recommendations [19]:

1. The EGJ complex should be measured during quiet respiration during the baseline recording in a segment that is comparatively free of swallowing and/or recording artifacts.
2. Intragastric pressure should be measured below the CD over three complete respiration cycles and if possible on the same segment being used to measure EGJ-CI.
3. LES-CD separation is the separation between the CD and LES signals at the time of inspiration. On exhalation, the precise location of the LES can be determined in blocked cases.
4. The RIP is the point along the axial axis where the inspiratory change in pressure changes from an inspiratory increase (characteristic of intra-abdominal recordings) to an inspiratory decrease (characteristic of intrathoracic recordings).

5. There are three different subtypes of EGJ pressure topography.

- No hiatal hernia: LES-CD separation 1 cm
- Hiatal hernia, distal RIP: LES-CD separation of more than 1 cm and RIP between the LES and CD
- Hiatal hernia, proximal RIP: LES-CD separation of more than 1 cm and RIP close to the LES

6. In the normal state (EGJ subtype 1), the RIP identifies the proximal margin of the LES-CD (EGJ) complex.

7. The RIP with hiatus hernia can localize either between the LES and CD or close to the LES.

8. The RIP location and relationship to LES may not be accurate for LES-CDs larger than 3 cm. But typically, the EGJ in these patients is dysfunctional.

9. The EGJ-CI should be expressed in mmHg.cm and referenced to intragastric pressure.

Conclusion

The Chicago classification, known as CCv4.0, is an evolving system aimed at improving the diagnosis and management of EMDs. It divides these disorders into two main categories: EGJ outflow disorders (achalasia and EGJOO) and peristalsis disorders, including esophageal spasm (DES and HE) and esophageal hypomotility (absent contractile and IEM). CCv4.0 introduces standardized HRM protocols to enhance reliability and research collaboration. It incorporates single wet swallows and provocation tests to increase sensitivity and specificity. Achieving a conclusive diagnosis involves both manometric and non-manometric evaluations. The definition of IEM now includes fragmented peristalsis. CCv4.0 no longer uses major and minor classifications but distinguishes EGJ outflow disorders from peristalsis disorders. Baseline metrics for EGJ are proposed including LES-CD, EGJ-CI, intragastric pressure, and respiratory inversion point. Although CCv4.0 is more accurate, ongoing research is needed to address certain areas like EGJ barrier function and inconclusive categorization of motility disorders and improve diagnosis and management strategies.

Author Confirmation

It is hereby confirmed that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all of us.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics Statement

The research was deemed as low risk and as such was reviewed by the Low-Risk Ethical procedure at the Faculty of Life Science and Education, University of South Wales, and granted approval.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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