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How Updates in Chicago Classification Impact Clinical Practice

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Abstract

Chicago Classification version 4.0 (CC v4.0), published in 2021, presents several modifications largely aimed at minimizing over-diagnosis of inconclusive patterns on high-resolution manometry (HRM). These include: 1) introduction of a standardized HRM protocol for consistency among centers, 2) emphasis on the need for supportive data in instances of inconclusive manometric patterns, 3) required presence of relevant symptoms in certain instances to reduce over-diagnosis and inappropriate interventions, and 4) classification as disorders of EGJ outflow or disorders of peristalsis. These updates aim to improve the clinical application of HRM and patient outcomes.

Keywords

achalasia; esophagus; esophageal motility; distal esophageal spasm; ineffective esophageal motility; manometry; per-oral endoscopic myotomy

Evolution of the Chicago Classification

The Chicago Classification (CC), is now in its fourth iteration [1]. As with previous iterations, CCv4.0 reflects the experience and deliberations of the International High-Resolution manometry (HRM) Working Group aimed at standardizing the management of esophageal motility disorders. The CC began in Paris in 2007 as an idea of John Pandolifino, Arjan Bredenoord, and Mark Fox to form an international collaboration to promote advancement in HRM diagnostics [2]. Inspired by the seminal contributions of Ray E. Clouse (1951–2007) who pioneered the development of HRM, the group decided to cooperatively build the International High-Resolution Manometry Working Group leading to the 2008 inaugural meeting of the Group in San Diego and CCv1.0 in 2009. The CC was conceptualized as a standardized approach to the interpretation of clinical HRM studies. In adopting a standardized nomenclature, objective metrics, and a structure based on physiological principles, CC has spurred a tremendous amount of research and collaboration resulting in an evolving schema open to refinement and revision. Most notable in CC

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Version 1.0 was inclusion of the integrated relaxation pressure (IRP), a then-novel metric whose central place in the understanding and quantification of esophagogastric junction (EGJ) relaxation has endured. The IRP was defined as the average pressure during the 4 seconds of maximal relaxation within the 10 s relaxation window after a swallow [3]. Also novel at the time, esophageal contractile vigor was quantified by the distal contractile integral (DCI), a measure of pressure across time and space [4]. Applying these parameters, version 1.0 of the CC described three types of achalasia, differentiated by their associated esophageal pressurization patterns, and EGJ outflow obstruction (EGJOO) wherein there was an elevated IRP along with some preserved peristalsis. Thus, the CC Version 1.0 pioneered the standardization and dissemination of the classification of esophageal motor disorders based on HRM.

The first major CC update (CCv2.0) followed from a meeting of the International HRM Working Group in Ascona in 2011 [5]. A prominent update with v2.0 was clarifying the subtyping of achalasia into type I (classic), type II (characterized by panesophageal pressurization (PEP)), and type III (spastic), with the inclusion of EGJOO as a possible variant of achalasia. A second development was the emergence of distal latency (DL) as a metric for defining spastic (premature) contractions, replacing pressurization velocity as the defining criterion. This change stemmed from a study by Pandolfino and colleagues, demonstrating that patients with high contractile front velocity or rapid contractions varied widely in terms of symptoms and motor diagnoses, with the majority actually having weak peristalsis or being normal [6]. In contrast, patients with short DL values, signifying premature contractions, always had dysphagia, either in the context of spastic achalasia or, less commonly, distal esophageal spasm (DES).

An expanded International HRM Working Group met in Chicago in conjunction with DDW 2014 to formulate the CC v3.0 that was formally presented at Ascona II in 2015 [7]. By this time, the CC was being used worldwide. CCv3.0 contributed detailed descriptions of EGJ morphology and streamlined criteria for peristaltic disorders to ease clinical application. Cutoffs for DCI were utilized to define failed peristalsis (<100 mmHg•s•cm), weak peristalsis (100–450 mmHg•s•cm), and hypercontractile peristalsis (>8000 mmHg•s•cm). The practice of using the term hypertensive peristalsis to describe swallows with DCI values between 5000–8000 mmHg•s•cm was discontinued, given its unclear clinical significance.

With expansions in the clinical and research applications of HRM along with the emergence of novel therapies for achalasia, the core International HRM Working Group agreed to proceed with a CC update in 2019. To foster development of a classification scheme generalizable across regions, representatives from six societies within the Federation of Neurogastroenterology and Motility from around the world were elected. This resulted in a diverse 52-member working group, representing 20 countries across five continents. At the onset, working group members were polled regarding their experience with CC v3.0 and priority areas for updating. Seven priorities emerged: 1) standardization of the clinical HRM study protocol, 2) refinement of criteria for EGJOO, 3) updating the subtyping of achalasia, 4) updating DES, 5) updating hypercontractile esophagus, 6) refinement of criteria for ineffective esophageal motility (IEM), and 7) providing guidance on the assessment of EGJ barrier function. A subgroup was formed for each of these priorities tasked with

generating a technical review and a series of statements to be put before the entire HRM working Group to accept or reject. The outputs of that process will be summarized herein.

CC v4.0 broadly classifies esophageal motility disorders on HRM as either disorders of EGJ outflow, or disorders of esophageal peristalsis (Figure 1). With regard to updates from prior CC iterations, diagnoses of achalasia and absent contractility have largely remained unchanged. EGJOO, IEM, and fragmented peristalsis underwent considerable redefinition. The manometric criteria for diagnoses of DES and hypercontractile esophagus are largely unchanged but both diagnoses now require concomitant symptoms of dysphagia and/or non-cardiac chest pain in order to meet criteria for clinical relevance. Furthermore, emphasizing that HRM diagnoses do not always equate to actionable pathology, a key priority of CC v4.0 was to emphasize the importance of supportive data beyond HRM (e.g. provocative maneuvers and/or adjunctive diagnostic tests) in certain scenarios to increase diagnostic confidence and guide clinical decision making. In addition, all recommendations articulated in CCv4.0 were formulated utilizing the formal RAND Appropriateness Method and, when feasible, evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process to assess the quality of supportive evidence.

Standardized HRM Protocol

A standardized HRM protocol was developed in CC v4.0 by which to apply and interpret clinical HRM studies [8] (Figure 2). The International HRM Working Group agreed that the basic protocol of 10 supine wet swallows is often insufficient to guide management, prompting recommendation for the routine inclusion of provocative maneuvers. Specifically, the proposed protocol includes wet swallows in both the supine and upright positions, as well as at least one supine multiple rapid swallow (MRS) sequence, and an upright rapid drink challenge (RDC). However, in certain scenarios, it was deemed reasonable to limit the testing protocol to 10 supine *or* 10 upright wet swallows, e.g. in clear-cut cases of achalasia. The CC v4.0 also highlights the utility of ancillary maneuvers such as the RDC and solid food swallows to elicit evidence of outflow obstruction and to elicit symptoms. If clinically suspected, postprandial HRM studies (preferably with impedance sensors) may also be helpful to identify rumination.

EGJ Outflow Obstruction

CC v4.0 brings major revisions in the diagnosis and characterization of EGJOO, a common but heterogenous diagnosis with CC v3.0 [9]. As before, a diagnosis of EGJOO should be considered when the median IRP is elevated, but esophageal body peristalsis is sufficiently intact to exclude achalasia. However, while some cases of EGJOO represent variant or evolving achalasia and should be managed accordingly, a substantial proportion are unrelated to LES dysfunction, instead representing effects of artifact, sliding hiatal hernia, mechanical obstruction, opioid induced esophageal dysfunction (OIED), etc. Consequently, interventions to disrupt the LES are not appropriate for most cases of EGJOO. Irreversible interventions such as laparoscopic or endoscopic myotomy should be reserved for a carefully selected, well characterized subgroup.

Given the problem of EGJOO over-diagnosis encountered with CC v3.0, a major intent of CC v4.0 was to refine the identification of actionable EGJOO. New criteria stipulate an elevated IRP in *both* supine and upright positions as well as at least 20% of wet supine swallows with intrabolus pressurization (without meeting criteria for achalasia). Isolated elevations in supine IRP (with normal upright IRP) or upright IRP (with normal supine IRP) are inconclusive. Furthermore, a manometric diagnosis of EGJOO is always clinically inconclusive, requiring that there also be relevant symptoms of dysphagia and/or non-cardiac chest pain and supportive evidence of obstructive physiology from a non-HRM test such as a timed barium esophagram (TBE), preferably with a tablet, or functional luminal imaging probe (FLIP) study. Responses to provocative maneuvers, such as outflow obstruction and esophageal pressurization with RDC or outflow obstruction with a solid test meal also constitute supportive evidence for actionable EGJOO.

CC v4.0 also encourages the description of EGJOO in the context of the associated esophageal body contraction pattern. Specifically, EGJOO may be described with normal peristalsis or with spastic, hypercontractile, or ineffective motility. However, the distinction between type III achalasia and EGJOO with spastic contractions can be challenging and depends on the presence of some “normal” peristalsis. Likewise, EGJOO with hypercontractile swallows may represent reactive hypercontractility to mechanical EGJ obstruction or the hypercontractility may represent a primary disorder of peristalsis also involving the LES. In contrast, diagnoses of EGJOO with ineffective motility or with normal peristalsis are more likely to represent a manifestation of reflux physiology or a normal variant, especially if there is minimal intrabolus pressurization or PEP. In brief, supportive testing is always warranted for further characterization of EGJOO to guide clinical management.

Achalasia

The criteria for achalasia types I and II are consistent with prior CC iterations requiring an elevated median IRP (either in the supine and/or upright position) and 100% failed peristalsis (Figure 3). PEP remains a defining feature of type II achalasia, although CC v4.0 notes that the distinction between type I and II can be somewhat arbitrary and not necessarily predictive of distinct treatment outcome aside from extreme cases with minimal esophageal pressurization, severe esophageal dilatation, or sink-trap deformity. On the other hand, very high levels of pressurization within PEP may represent embedded esophageal spasm potentially masking type III achalasia. CCv4.0 notes several scenarios that may shift interpretation of HRM towards an inconclusive diagnosis of types I or II achalasia, warranting supportive testing to guide management, such as with a TBE and/or FLIP. Specifically, 1) 100% absent contractility with IRP values near the upper limits of normal in both the supine and upright positions, or 2) evidence of peristalsis with changing patient position in a pattern otherwise consistent with types I or II achalasia, may be inconclusive for achalasia.

Type III achalasia requires an elevated median IRP (either in the supine and/or upright positions) with spasm (premature contraction), defined as DL <4.5 s with DCI >450 mmHg•s•cm in at least 20% of wet swallows. Although prior iterations of the CC were

ambiguous as to whether a diagnosis of type III achalasia required 100% failed peristalsis, CC v4.0 clearly requires 100% absent peristalsis (defined as either failed peristalsis or spasm). Therefore, per CCv4.0, patients who have an elevated IRP, elevated intrabolus pressurization, and swallows with a mixture of spasm and “normal” peristalsis meet criteria for EGJOO with spastic contractions rather than a conclusive diagnosis of type III achalasia. Greater proportions of test swallows with spasm increases confidence in managing these as type III achalasia. Per-oral endoscopic myotomy (POEM) with extension of the myotomy proximally, tailored to the length of the spastic segment, is the generally accepted first-line treatment for type III achalasia, given superior outcome compared to therapies achieving only LES disruption. CC v4.0 acknowledges that OIED can mimic type III achalasia, and that HRM studies should be done withholding opioids if possible, based on medication half-life. Given their potential reversibility, cases of OIED should be directed toward opioid cessation and conservative interventions if possible.

Disorders of Peristalsis

Following the algorithmic classification of CC v4.0, a disorder of peristalsis should be considered if the median IRP is normal, or if the median IRP is elevated but criteria for an actionable diagnosis of EGJOO are not met. Consistent from CC v3.0, disorders of peristalsis may include absent contractility, DES, hypercontractile esophagus, and IEM (Table 1). Fragmented peristalsis was eliminated and merged with IEM. CC v4.0 also implements a hierarchical classification among disorders of peristalsis, with DES prioritized first, then hypercontractile esophagus, and finally IEM, acknowledging potentially overlapping features.

Absent Contractility—The criteria for absent contractility remain unchanged for CC v4.0 (Figure 4a), with a conclusive diagnosis requiring normal median IRP in the supine and upright positions and 100% failed peristalsis (DCI <100 mm Hg•s•cm). Version 4.0 points out that for cases meeting criteria for absent contractility with a median IRP near the upper limit of normal (i.e., supine IRP of 10 to15 mmHg on the Medtronic system), particularly in patients with prominent dysphagia, it is necessary to consider type I achalasia as an alternative diagnosis. Manometric provocative maneuvers (such as RDC, solid test meal) and/or adjunctive modalities (such as TBE, FLIP) help to make this critical distinction.

Distal Esophageal Spasm—As in CC v3.0, CC v4.0 maintains the criterion of ≥20% test swallows with premature contractions (DL <4.5 seconds) for a diagnosis of DES [10] (Figure 5). However, the manometric finding is deemed inconclusive without the presence of dysphagia and/or non-cardiac chest pain to make it clinically relevant. Premature contractions must also exhibit a DCI >450 mmHg•s•cm to be classified as spastic. As such, DES is an exceedingly rare finding with most suspected cases being type III achalasia. Similar to the distinction between EGJOO with spastic features and type III achalasia, greater proportions of spastic test swallows and prominent dysphagia and/or chest pain increase the confidence in the diagnosis of DES as a primary disorder of peristalsis. Alternatively, a significant proportion of DES patterns may represent a secondary response to gastroesophageal reflux. Further data are warranted to better distinguish actionable phenotypes of manometric DES.

Hypercontractile Esophagus—A subtle modification in CC v4.0 was to make jackhammer esophagus a subtype of hypercontractility rather than considering the two synonymous [11] (Figure 5 B–D). This highlights the importance of ruling out mechanical obstruction at the distal esophagus or EGJ as a cause of a reactive hypercontractile response. Furthermore, consistent with the hierarchical organization of disorders of peristalsis, the criteria for type III achalasia or DES cannot be present. Consequently, CC v4.0 requires ≥20% hypercontractile swallows (DCI >8000 mmHg•s•cm) in the supine position and symptoms of dysphagia and/or non-cardiac chest pain for an actionable diagnosis of hypercontractile esophagus. Also new in CC v4.0 hypercontractile esophagus is considered heterogeneous with three subtypes: 1) jackhammer with repetitive prolonged contractions (generally associated with greater DCI values and more profound symptoms), 2) single peaked hypercontractile swallows, and 3) hypercontractile swallows with a vigorous LES aftercontraction. In general CC v4.0 advises a more cautious management strategy to hypercontractile esophagus, particularly without jackhammer features. As with EGJOO, conservative medical therapy should be exhausted prior to consideration of myotomy.

Ineffective Esophageal Motility (Figure 5)—In addition to "upgrading" IEM and fragmented peristalsis from minor motility disorders (CC v4.0 does not differentiate between major and minor motility disorders), CC v4.0 combines these entities and applies more stringent criteria for an IEM diagnosis [12]. Specifically, CC v4.0 requires ≥70% of swallows to be ineffective (DCI <450 mmHg•s•cm) or fragmented (>5 cm break in the 20 mmHg isobaric contour of for swallows with DCI >450 mmHg•s•cm) for an IEM diagnosis. Alternatively, ≥50% failed swallows (DCI <100 mm Hg•s•cm) also constitutes IEM. If between 50% and 70% of swallows are ineffective, the study may be considered inconclusive for IEM. In such cases, poor bolus transit on impedance at HRM, absence of contractile reserve on MRS sequences, and/or poor transit on barium esophagram provide supportive evidence for IEM.

EGJ Barrier Metrics

In addition to defining and classifying motility disorders with greater reliability and accuracy, a major advantage of HRM lies in visualizing and quantifying EGJ barrier function as it pertains to both dysphagia and reflux disease. Compromised EGJ barrier function leads to excessive gastroesophageal reflux and, potentially, esophagitis. Hence, HRM metrics assessing EGJ integrity are clinically important. However, the EGJ is very complex comprised of both the crural diaphragm (CD) and LES component, each subject to independent control mechanisms and pathophysiology. No single metric can capture all attributes of EGJ barrier function. The working group considered several potential metrics of EGJ integrity including LES-CD separation, the EGJ contractile integral (EGJ-CI), the respiratory inversion point (RIP) and intragastric pressure [13]. Strong recommendations were made regarding LES-CD separation as indicative of hiatus hernia, but the numerical threshold for defining hiatal hernia was not agreed upon. There was also no agreement on the significance of the RIP, only that it could localize either above the LES or between the LES and CD in cases of hiatus hernia. There was agreement on how to measure the EGJ-CI and that it should be referenced to gastric pressure in units of mmHg•cm, but the reported numerical threshold indicative of a hypotensive EGJ varied widely among centers

and was not agreed upon. Similarly, intragastric pressure was endorsed as an important metric worthy of further study but there was no agreement on a numerical threshold indicative of abdominal obesity. In brief, while there was support for their quantification and further exploration, there was no agreement on the criteria defining abnormality for LES-CD separation, EGJ-CI, or intragastric pressure.

CONCLUSION

The CC is and will continue to be a work in progress with CC v4.0 representing the 2021 iteration. Consistent with its overarching objective of standardizing the diagnostic process and improving the management of esophageal motility disorders, CC v4.0 focused on the perceived weaknesses of CC v3.0 and implementing corrective changes. Several major modifications were made, largely aimed at minimizing over-diagnosis of manometrically inconclusive conditions. Specifically, CC v4.0: 1) introduces a standardized clinical HRM study protocol for consistency among centers; 2) emphasizes the need for and utility of supportive data in instances of inconclusive manometric diagnoses (both manometric, with provocative maneuvers, and non-manometric, with TBE and/or FLIP); 3) mandates the presence of relevant symptoms in instances of inconclusive diagnoses to reduce over-diagnosis and inappropriate interventions; 4) segregates disorders of EGJ outflow from disorders of peristalsis and eliminates a distinction between major and minor motility disorders, instead establishing a hierarchy of disorders of peristalsis; and 5) introduces more stringent criteria for the diagnoses of EGJOO, DES, hypercontractile esophagus, and IEM. Hopefully, these revisions will further improve the clinical application of HRM and patient outcomes. It is also envisioned that the gray zones identified in this iteration, most notably metrics of EGJ barrier function, will inspire future research which will in turn guide future iterations of the CC to build upon the refinements of CC v4.0.

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Peter J Kahrilas: Consultant: Ironwood Pharmaceuticals, Reckitt, Johnson & Johnson

Abbreviations:

CC	Chicago Classification
CD	Crural diaphragm
HRM	High-resolution manometry
IRP	Integrated relaxation pressure
DCI	Distal contractile integral

DES	Distal esophageal spasm
DL	Distal latency
EGJ	Esophagogastric junction
EGJ-CI	EGJ contractile integral
EGJOO	EGJ outflow obstruction
FLIP	Functional lumen imaging probe
GRADE	Grading of Recommendations Assessment; Development; and Evaluation
IEM	Ineffective esophageal motility
LES	Lower esophageal sphincter
MRS	Multiple rapid swallow
OIED	Opioid induced esophageal dysfunction
PEP	Panesophageal pressurization
POEM	Per-oral endoscopic myotomy
RDC	Rapid drink challenge
RIP	Respiratory inversion point
TBE	Timed barium esophagram

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Objectives

- To briefly summarize the Chicago Classification update
- To present the recommended standard esophageal high-resolution manometry protocol and barriers to widespread implementation
- To discuss the renewed focus on clinical symptoms
- To predict the impact of revisions on surgery and gastroenterology clinical practice

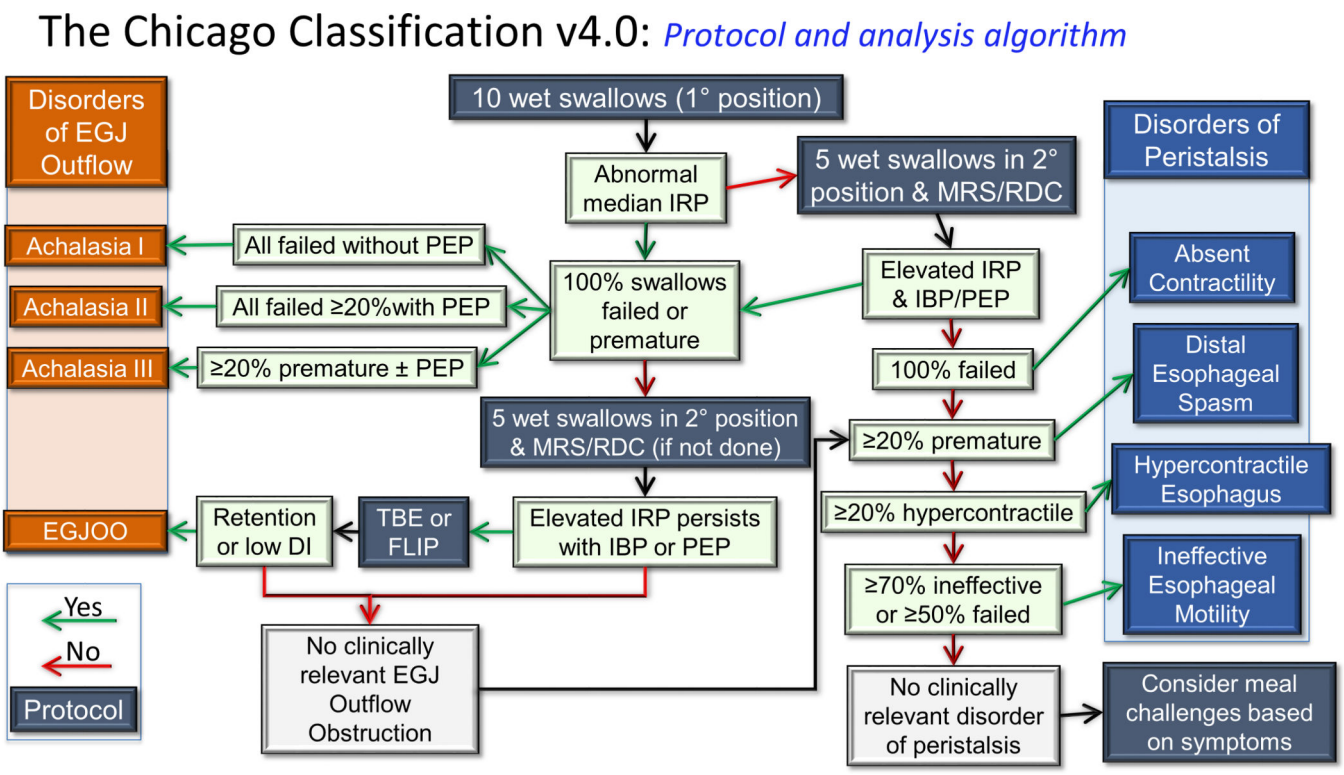
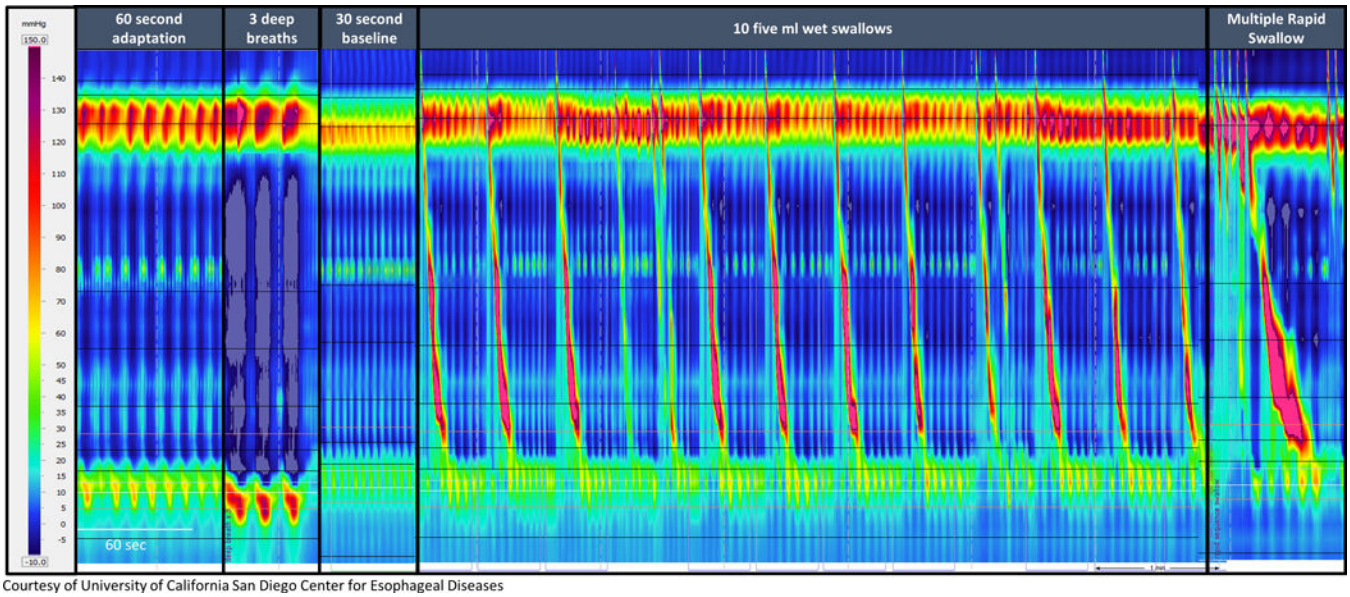


Figure 1.

The CC v4.0. Disorders of EGJ outflow are segregated from disorders of peristalsis acknowledging that overlap does exist in some cases. The standardized protocol is built in to the schema emphasizing the need for additional maneuvers or supportive testing in some instances.



Courtesy of University of California San Diego Center for Esophageal Diseases

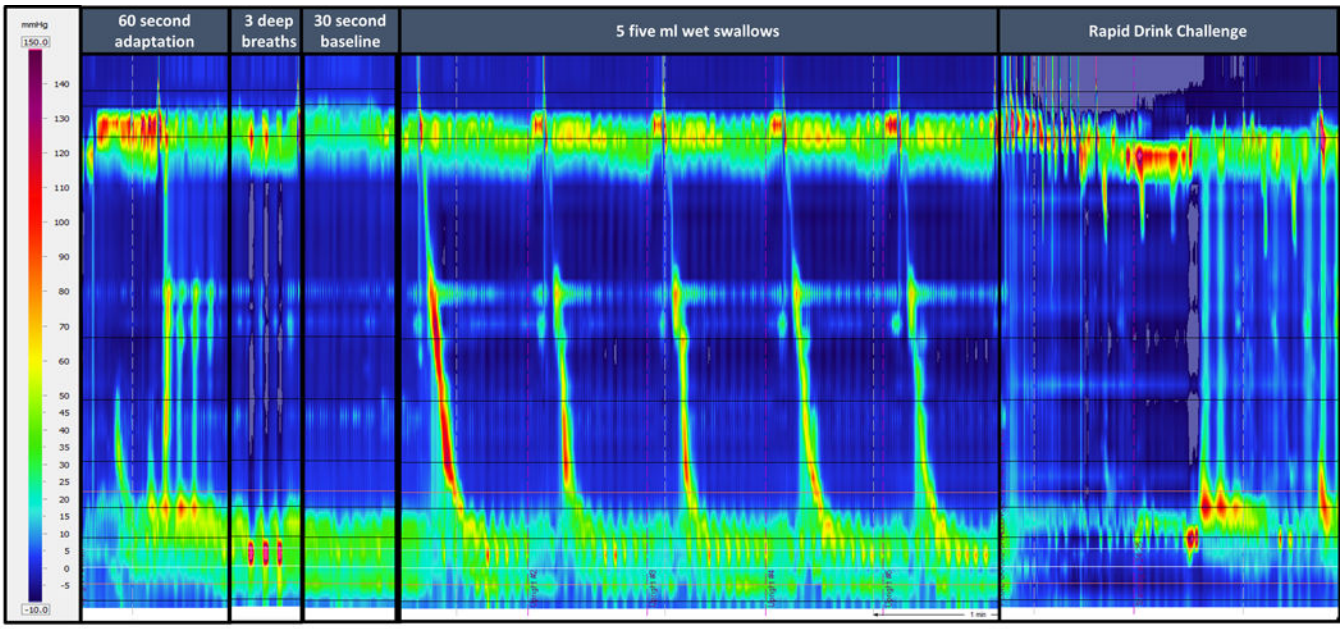


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Figure 2.

Figure 2a: Protocol in Supine Position

Figure 2b: Protocol in Upright Position

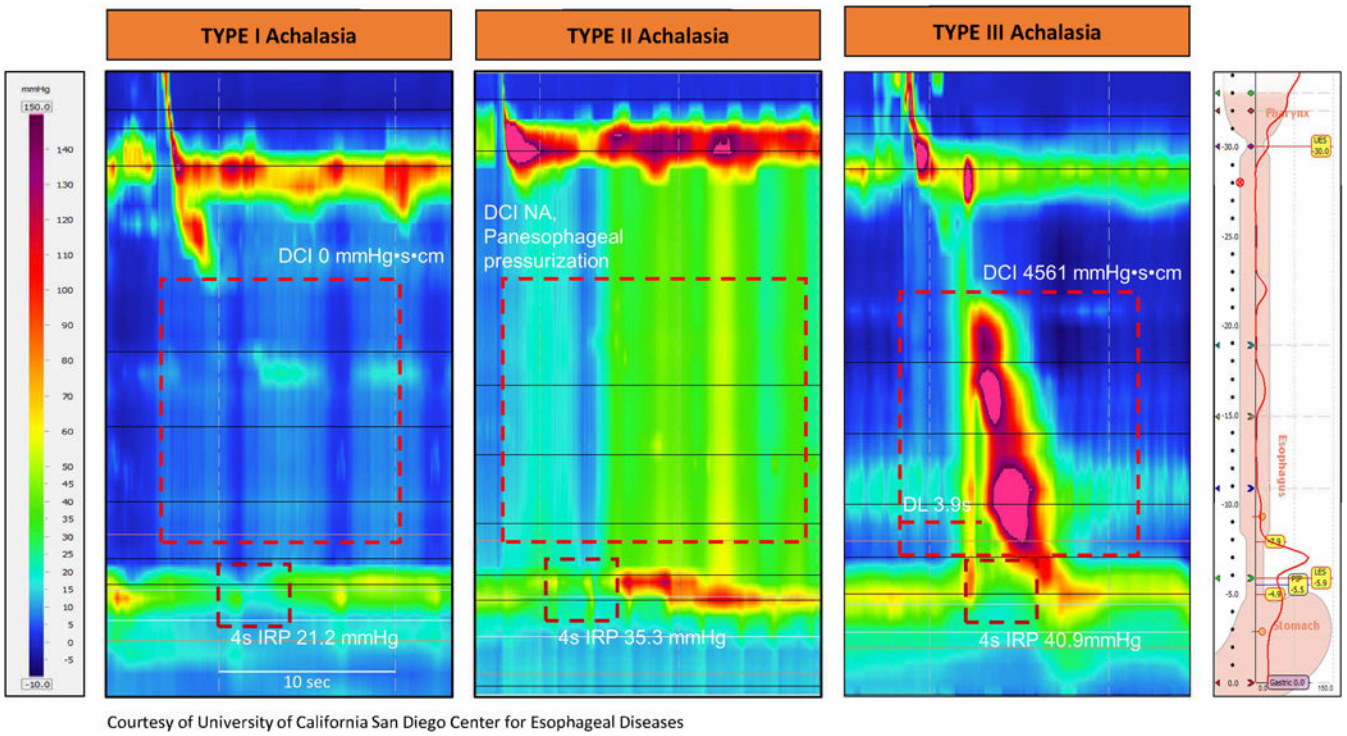

Figure 3.
Achalasia Subtypes.

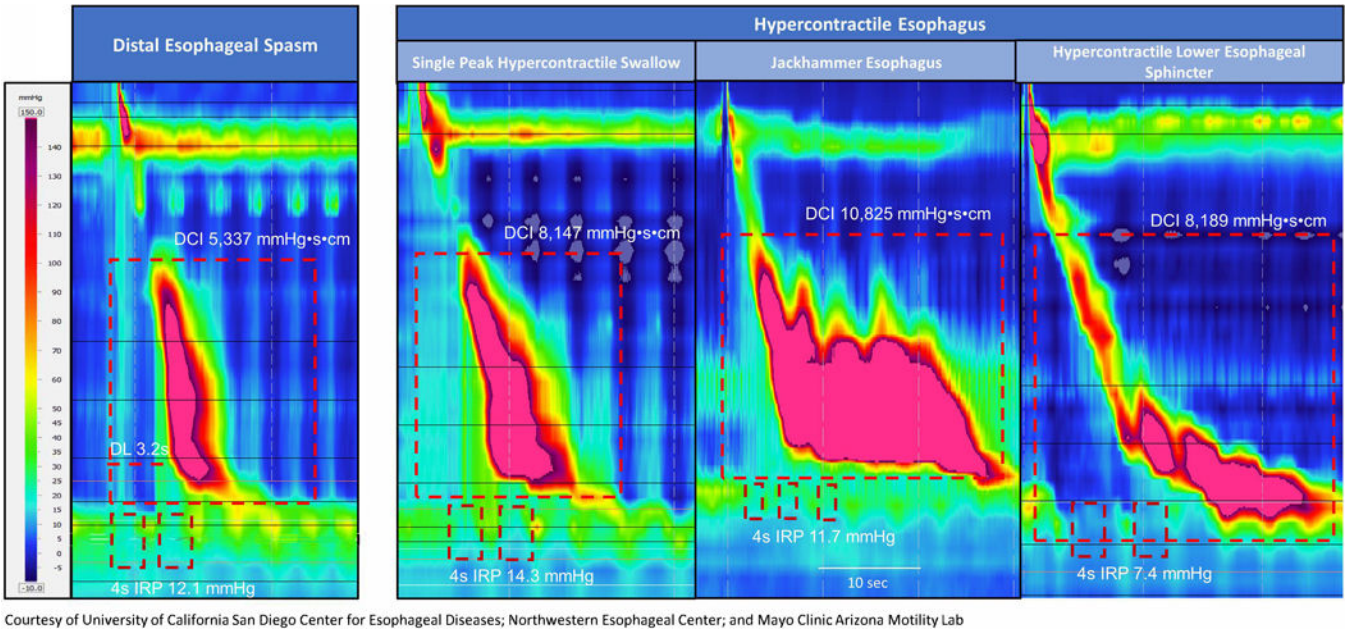

Figure 4.
Disorders of peristalsis with Esophageal Spasticity or Hypercontractility.

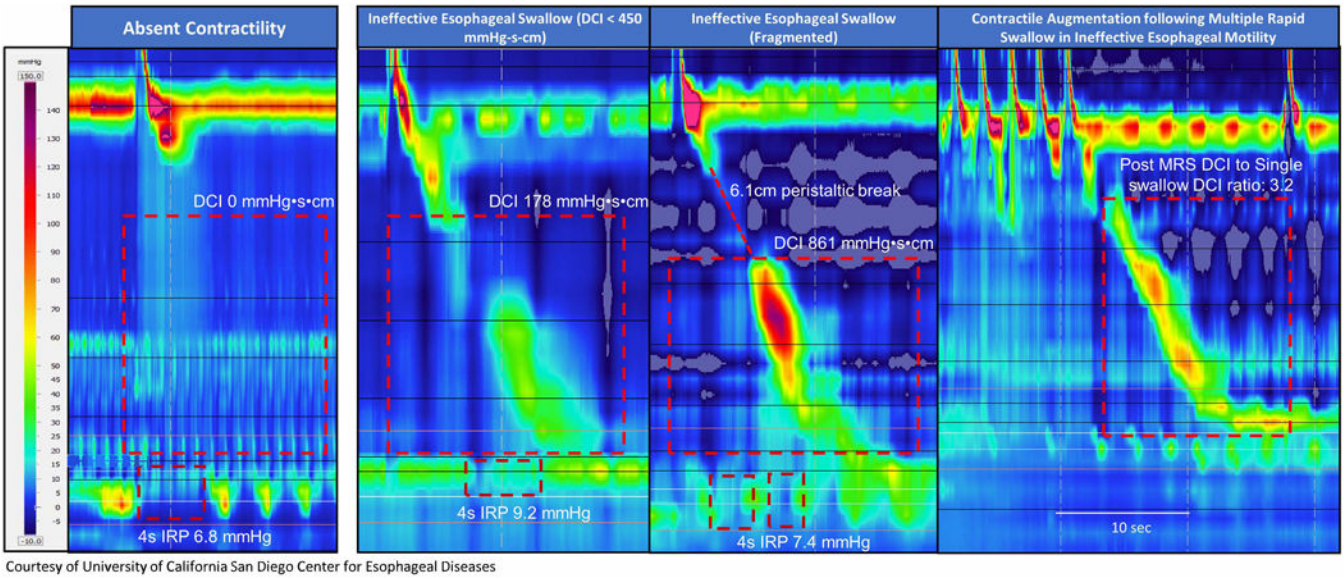

Figure 5.
Disorders of peristalsis with Reduced Contractile Vigol or Contiguity of peristalsis.

Table 1.

Disorders of Esophageal Peristalsis

Diagnosis	**CC v4.0 Criteria of Normal Median IRP *AND:***	**Additional Considerations**
Absent Contractility	100% failed peristalsis	Borderline median IRP values should prompt consideration of type I achalasia, especially if prominent dysphagia
Distal Esophageal Spasm (DES)	≥20% of swallows with premature contraction (distal latency <4.5 seconds) in setting of dysphagia and/or non-cardiac chest pain symptoms	≥20% of swallows with premature contraction but DCI <450 mmHg•s•cm is inconclusive for manometric diagnosis of DES
Hypercontractile Esophagus	≥20% of swallows with hypercontractility (DCI >8000 mmHg•s•cm) in setting of dysphagia and/or non-cardiac chest pain symptoms	Must rule out distal esophageal/EGJ mechanical obstruction; three sub-types (single-peaked hypercontractile swallows, jackhammer with repetitive prolonged contractions, hypercontractile swallows with vigorous LES after-contraction)
Ineffective Esophageal Motility (IEM)	>70% of swallows ineffective (DCI <450 mmHg•s•cm) and/or fragmented (peristaltic break >5 cm in 20 mmHg isobaric contour with normal DCI), *or* ≥50% swallows failed (DCI <100 mmHg•s•cm)	50–70% of swallows ineffective is inconclusive for diagnosis of IEM and should prompt supportive data (poor bolus transit on impedance or barium esophagram, lack of contraction reserve on multiple rapid swallow sequences)