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TECHNICAL NOTE

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Chicago Classification update (V4.0): Technical review on diagnostic criteria for ineffective esophageal motility and absent contractility

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Abstract

Esophageal hypomotility disorders manifest with abnormal esophageal body contraction vigor, breaks in peristaltic integrity, or failure of peristalsis in the context of normal lower esophageal sphincter relaxation on esophageal high-resolution manometry (HRM). The Chicago Classification version 4.0 recognizes two hypomotility disorders, ineffective esophageal motility (IEM) and absent contractility, while fragmented peristalsis has been incorporated into the IEM definition. Updated criteria for ineffective swallows consist of weak esophageal body contraction vigor measured using distal contractile integral (DCI, 100–450 mmHg·cm·s), transition zone defects >5 cm measured using a 20 mmHg isobaric contour, or failure of peristalsis (DCI < 100 mmHg·cm·s). More than 70% ineffective swallows and/or ≥50% failed swallows are required for a conclusive diagnosis of IEM. When the diagnosis is inconclusive (50%–70% ineffective swallows), supplementary evidence from multiple rapid swallows (absence of contraction reserve), barium radiography (abnormal bolus clearance), or HRM with impedance (abnormal bolus clearance) could support a diagnosis of IEM. Absent contractility requires 100% failed peristalsis, consistent with previous versions of the classification. Consideration needs to be given for the possibility of achalasia in absent contractility with dysphagia despite normal IRP, and alternate complementary tests (including timed upright barium esophagram and functional lumen imaging probe) are recommended to confirm or refute the presence of achalasia. Future research to quantify esophageal bolus retention on stationary HRM with impedance and to understand contraction vigor thresholds that predict bolus clearance will provide further refinement to diagnostic criteria for esophageal hypomotility disorders in future iterations of the Chicago Classification.

KEYWORDS
absent contractility, high-resolution manometry, ineffective esophageal motility

Key Points

- Diagnostic criteria for ineffective esophageal motility have been made more stringent, now requiring >70% ineffective swallows and/or ≥50% failed swallows.
- Fragmented swallows are now part of the ineffective spectrum, and fragmented peristalsis has been removed as a motility diagnosis.
- Criteria for absent contractility remain 100% failed swallows with normal relaxation of the lower esophageal sphincter.

1 | INTRODUCTION

Esophageal hypomotility consists of abnormal contraction vigor, large breaks in peristaltic integrity, or failure of peristalsis on manometry, with normal lower esophageal sphincter (LES) relaxation.[1–3] The Chicago Classification was developed as a hierarchical algorithm for characterization of esophageal motor disorders, within which the criteria for diagnosis of hypomotility disorders have evolved over time. Chicago Classification version 3.0 (CCv3.0) included three motor disorders with esophageal hypomotility: absent contractility, ineffective esophageal motility (IEM), and fragmented peristalsis.[1] The most current version, Chicago Classification version 4.0 (CCv4.0), was recently published by the International HRM Working Group of 52 members, following a 2-year period of development.[3] While criteria for absent contractility were maintained in CCv4.0, fragmented peristalsis was no longer designated an independent motor disorder, but was instead incorporated into the IEM definition, within more stringent IEM diagnostic criteria.[3] This technical review describes these changes and discusses literature supporting the new criteria.

2 | METHODS

As part of the development of CCv4.0, one working group consisting of seven members was dedicated to esophageal hypomotility disorders. This working group, led by two co-chairs, was tasked with developing statements regarding a conclusive definition of IEM, and describing further testing supporting a clinical diagnosis of IEM based on literature review and expert consensus. Existing criteria for absent contractility were also reviewed, but no new statements were generated since the working group determined that the existing diagnostic criteria did not need to be updated. As detailed in the main CCv4.0 document, each proposed statement underwent two rounds of independent ranking by the entire CCv4.0 working group according to the RAND UCLA Appropriateness Methodology

TABLE 1 Chicago Classification version 4.0: Statements Endorsed by the International HRM Working Group

Recommended statement	Percent agreement	Strength of recommendation	Level of Evidence*
The diagnostic classification "fragmented peristalsis" should be removed. This concept should be incorporated into the overall diagnosis of IEM	8	86%	Very Low
A swallows with a DCI <450 mmHg·cm·s is consistent with an ineffective swallow	8	91%	
A transition zone defect >5 cm is consistent with an ineffective swallow	7	74%	
A conclusive diagnosis of IEM requires >70% ineffective swallows or ≥50% failed peristalsis	8	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	7	80%	Very Low
Supportive testing for IEM could include poor bolus transit on impedance or barium esophagography	7	80%	Very Low
Supportive testing for IEM could include lack of contraction reserve on multiple rapid swallow	8	80%	Very Low

Abbreviations: DCI, distal contractile integral; IEM, ineffective esophageal motility.

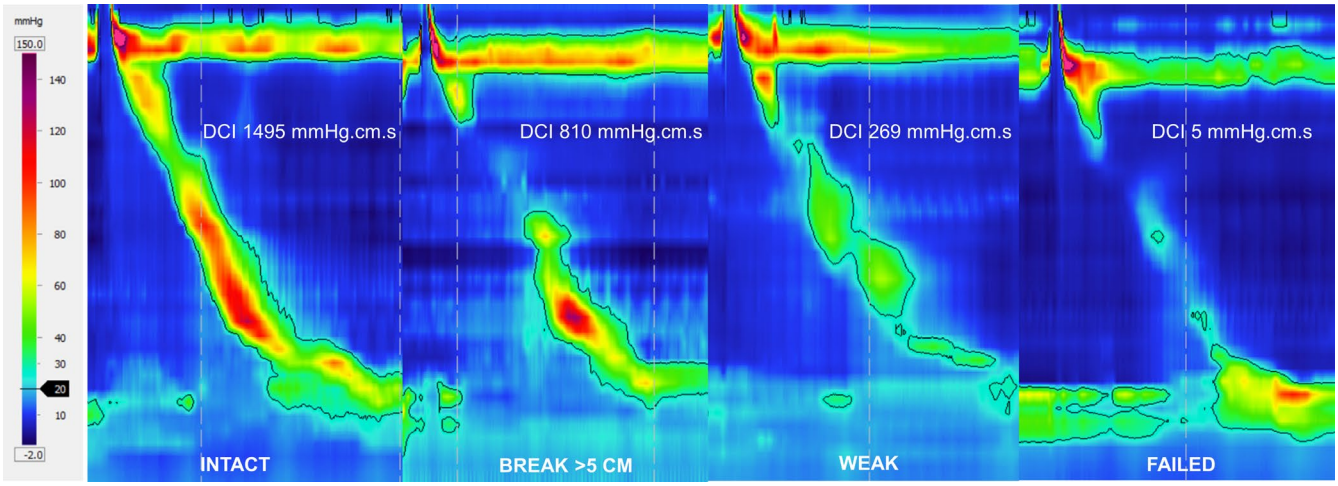

FIGURE 1 Peristaltic patterns on esophageal high-resolution manometry that can be encountered in hypomotility disorders. Esophageal body contraction vigor is assessed using distal contractile integral (DCI). Integrated relaxation pressure (IRP) and distal latency (DL) are normal in ineffective swallows. Intact swallow: DCI>450 mmHg·cm·s. Large breaks: using a 20 mmHg isobaric contour, distance between skeletal and smooth muscle contraction segments is >5 cm. Weak swallow: DCI 100–450 mmHg·cm·s. Failed swallow: DCI<100 mmHg·cm·s. Swallows with large breaks, weak swallows, and failed swallows are considered ineffective swallows. Ineffective esophageal motility requires >70% ineffective swallows and/or ≥50% failed swallows for a conclusive diagnosis. Absent contractility is diagnosed when 100% of swallows fail

to determine appropriateness of each statement. Statements with ≥85% agreement as appropriate were considered strong recommendations, while those with 80 to 85% agreement as appropriate were considered conditional recommendations (Table 1). Statements nearly meeting criteria and/or those generating controversy were discussed at working group meetings. Additionally, statements that met criteria for inclusion in the final CCv4.0 underwent further independent evaluation to assess the level of supportive evidence, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process, when possible.[4] Two experts external to the working sub-groups independently evaluated the supportive literature provided by the sub-groups. Some statements were not amenable to the GRADE process, either because of the structure of the statement or lack of available evidence. This technical review reports the statements proposed by the CCv4.0 working group to update the definition of esophageal hypomotility disorders, particularly IEM.

3 | HRM METRICS AND DIAGNOSTIC CRITERIA

Individual smooth muscle peristaltic sequences following 5 ml supine test swallows have been characterized on high-resolution manometry (HRM) based on LES function, esophageal body contraction vigor, timing of peristalsis, and integrity of peristaltic contour. The integrated relaxation pressure (IRP) is used to determine adequacy of LES relaxation, and upper limits of normal are dependent on the HRM system utilized.[3,5] Contraction vigor is evaluated using distal contractile integral (DCI), which takes into account the amplitude, length, and duration of the smooth muscle contraction segments in the esophageal body. Esophageal body contraction amplitude of 30 mmHg was established as the threshold above which adequate bolus transit occurred on concurrent manometry and fluoroscopy.[6] Comparative HRM studies determined that this threshold amplitude corresponds to a DCI value of 450 mmHg·cm·s.[1,7] Distal latency (DL) measures timing of peristalsis, and the upper limit of normal is 4.5 s.[8] Peristaltic integrity is assessed using a 20 mmHg peristaltic contour, and breaks larger than 5 cm are demonstrated to be clinically significant in their association with bolus escape on HRM with impedance.[9]

Using DCI as a measure of contraction vigor, ineffective swallows were defined on CCv3.0 as swallows with DCI < 450 mmHg·cm·s (Figure 1).[1] Ineffective swallows could be weak (DCI 100–450 mmHg·cm·s) or failed (DCI < 100 mmHg·cm·s). Fragmented swallows had >5 cm breaks in peristaltic integrity with intact DCI values (450 mmHg·cm·s). Any combination of failed or weak swallows reaching ≥50% defined IEM according to CC v3.0. A diagnosis of absent contractility required 100% failed swallows. Fragmented peristalsis consisted of ≥50% swallows with fragmented swallows.[1]

4 | LIMITATIONS OF CCv3.0

With advancing clinical applications and research investigations in the past 5 years, several limitations were identified with CCv3.0 diagnostic criteria, especially within hypomotility disorders. First, fragmented peristalsis was extremely rare in many reports. Despite this, large breaks in peristaltic integrity measuring >5 cm have been demonstrated to be relevant in retention of swallowed bolus[9] and abnormal reflux clearance measured using esophageal acid exposure time (AET) on ambulatory reflux monitoring.[10] Second, both weak (DCI

TABLE 2 Physiologic provocative tests useful as supportive evidence in hypomotility disorders

Test	Technique	Median IRP (IQR)	Normal contraction response	Outflow obstruction	Other abnormal findings
Multiple Rapid Swallows (MRS)	Five 2 ml water swallows administered using a syringe in rapid succession while supine; 3 sets of MRS provides consistent results	1.6 (0.3–2.4) mmHg	DCI following MRS higher than mean non-failed single swallow DCI Ratio of MRS DCI:single swallow DCI>1 indicates contraction reserve	MRS is not utilized to diagnose latent EGJ obstruction	Peristaltic or non-peristaltic contraction sequences during swallows indicates abnormal deglutitive inhibition
Rapid Drink Challenge (RDC)	100–200 ml water administered through a straw as fast as possible while upright	2.0 (0.8 to 2.9) mmHg	Similar to MRS interpretation, but contraction response is not consistently seen even in healthy volunteers	RDC IRP>12 mmHg	Esophageal pressurization, shortening, and/or high trans-EGJ gradient indicates obstructive process at EGJ; symptom provocation during RDC
Solid Test Meal (STM), with or without post-prandial monitoring	Various test meals adapted to local availability and cuisine (e.g. 100–200 g of soft cooked long grain rice, cheese, and onion pasty); optional post-prandial monitoring for 30–60 min	6.1 (4.8–8.5) mmHg	No standardized interpretation of augmentation of contraction response	STM IRP>25 mmHg	Similar to RDC; symptom provocation during STM; rumination or supragastric belching episodes identified during post-prandial monitoring

Abbreviations: DCI, distal contractile integral; EGJ, esophagogastric junction; IQR, inter-quartile range; IRP, integrated relaxation pressure.

100–450 mmHg·cm·s) and failed (DCI < 100 mmHg·cm·s) peristaltic sequences are considered ineffective, but bolus transit and reflux exposure implications of failed sequences are more profound.[11–13] Third, as many as 11%–17% of healthy volunteers fulfilled criteria for IEM using CCv3.0 criteria, thereby lowering the positive predictive value of these criteria for clinically relevant IEM in symptomatic patients.[5,14,15] Finally, the IEM diagnostic threshold of 50% ineffective swallows was demonstrated to be less discriminant of abnormal bolus transit and abnormal esophageal reflux burden compared to >70% ineffective swallows.[10,16,17]

5 | PROVOCATIVE TESTING

Provocative testing has emerged as a clinically useful tool as part of esophageal motility testing (Table 2). The simplest provocative test utilized in hypomotility disorders is multiple rapid swallows (MRS). When repetitive swallows are administered rapidly, there is profound inhibition of esophageal peristalsis and lower esophageal sphincter (LES) tone during the swallows, with an augmented contraction sequence following the final swallow of the sequence (Figure 2).[18,19] In healthy individuals, the DCI of the contraction sequence following MRS is typically higher than the mean DCI of non-failed single swallows, termed contraction reserve when the ratio of MRS DCI: single swallow DCI is more than 1.[19] This ratio is directly related to baseline impedance and effective chemical clearance at baseline[20] and following azithromycin administration.[21] The absence of contraction reserve in IEM has been linked to post-fundoplication dysphagia,[19,22] a higher likelihood of persistence or development of IEM over time,[23] and higher esophageal reflux burden on ambulatory reflux monitoring.[24]

Other provocative tests utilized in clinical esophagology include rapid drink challenge (RDC)[25,26] and solid test meal (STM).[15,27] The clinical utility of RDC lies in demonstration of latent EGJ obstruction, in the form of esophageal pressurization or increase in trans-EGJ pressure gradients during rapid drinking of 100–200 ml of water through a straw in the sitting position. Administration of a standardized meal during HRM can also demonstrate latent obstruction and augmentation of esophageal body contraction, although the test is limited because it is cumbersome, time-consuming, and the meal administered may not be similar across motility centers. Symptom analysis during provocative tests (both RDC and STM) may have adjunctive value in the evaluation of symptomatic patients, but recording and grading of symptoms have not been standardized to date.[15,28]

6 | CHANGES IN DIAGNOSTIC DESIGNATIONS AND CRITERIA WITH CCv4.0

The relatively infrequent identification of fragmented peristalsis and the clinical relevance of >5 cm breaks in peristaltic integrity prompted incorporation of fragmented swallows into the IEM diagnostic criteria, and elimination of fragmented peristalsis as an independent motor disorder in CCv4.0.[3] Since both IEM and absent

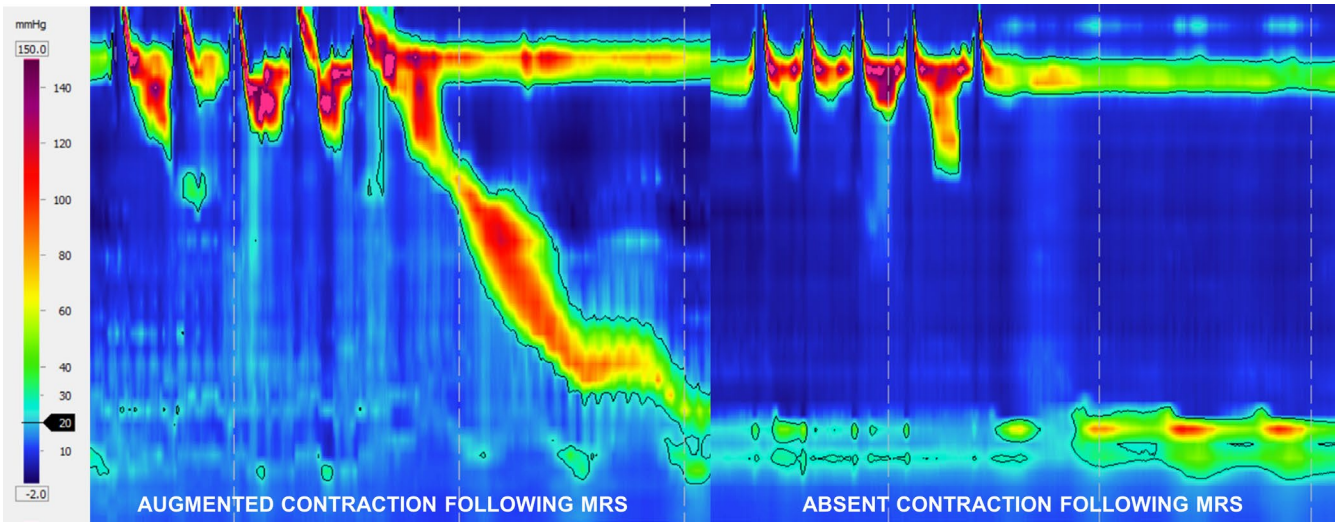

FIGURE 2 Provocative testing using multiple rapid swallows (MRS). Five 2 ml swallows are administered in rapid succession. There is profound inhibition of esophageal body contraction and LES tone during the swallows. Following the final swallow of the sequence, an augmented contraction sequence is seen in healthy individuals, with higher distal contractile integral (DCI) compared to the mean DCI from non-failed single swallows—this is termed presence of contraction reserve (left panel). If contraction is absent following the last MRS swallow, or if MRS DCI is less than mean single swallow DCI, contraction reserve is absent. Absence of contraction reserve is associated with a higher likelihood of post-fundoplication dysphagia, and higher esophageal acid burden under certain circumstances

contractility impair esophageal clearance, associate with reflux symptoms, and participate in the pathophysiology of GERD,[13,29–31] these conditions are considered together under the umbrella of hypomotility disorders. Esophageal hypomotility disorders are the most common motility findings in pH-metry proven GERD.[32,33]

7 | INEFFECTIVE ESOPHAGEAL MOTILITY

With removal of fragmented peristalsis as a diagnostic category, the presence of >5 cm breaks (independent of DCI value) is now included as a criterion of ineffective swallows and will count toward the ineffective swallow threshold in the diagnosis of IEM (Figure 1). With emerging evidence that >70% ineffective peristalsis is more relevant to abnormal bolus transit and more severe GERD phenotypes compared to 50%–70% ineffective swallows,[11,13,34] the diagnostic threshold for IEM was modified to require >70% ineffective swallows. In recognition of the more significant contribution of failed swallows to esophageal acid burden compared to ineffective swallows, a threshold of 50% was set for failed swallows as a diagnostic criteria of IEM.

7.1 | Conclusive diagnosis

A conclusive diagnosis of IEM requires more than 70% ineffective swallows (DCI 100 to 450 mmHg·cm·s or >5 cm transition zone defect in peristalsis), or at least 50% failed peristalsis (DCI < 100 mmHg·cm·s) (Very Low GRADE, Strong Recommendation).[9,12,17,35]

In reports involving 16 asymptomatic controls studied using HRM with impedance, presence of >5 cm defects in peristaltic integrity using a 20 mmHg isobaric contour was uniformly associated with abnormal bolus clearance.[9,35] The likelihood of incomplete bolus transit was highest with ≥70% ineffective swallows (sensitivity 85% and specificity 81%) and ≥30% failed swallows (sensitivity 85% and specificity 88%) in a mixed cohort of 81 symptomatic patients.[17]

In a study of 880 swallows from 88 IEM patients, failed swallows (DCI < 100 mmHg·cm·s) had an accuracy of 76% in predicting abnormal bolus transit, in contrast to 40% for weak swallows (DCI 100–450 mmHg·cm·s).[12] In another study of 188 symptomatic patients (25% with IEM) undergoing HRM and reflux monitoring, ≥50% failed swallows associated with abnormal distal AET to a significantly greater degree compared to similar proportions of weak swallows ($p \leq 0.04$ for each comparison).[36] In a multicenter study of 351 symptomatic patients, ≥50% failed swallows predicted abnormal total AET on both univariate and multivariable analysis ($p \leq 0.009$, and $p = 0.02$ respectively). In the same study, ≥70% ineffective swallows and ≥70% fragmented swallows separately predicted abnormal total AET on univariate analysis ($p \leq 0.01$ for each analysis) and trended toward significance on multivariable analysis ($p = 0.07$ for each).[10] Severe peristaltic dysfunction (>70% ineffective sequences) is also associated with esophageal mucosal injury,[10,13,37,38] and especially supine acid exposure.[34,39]

7.2 | Inconclusive diagnosis

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 (Very Low GRADE, Conditional Recommendation).[10,36]

Although sensitive, the 50% ineffective swallow threshold utilized in CCv3.0 for IEM diagnosis was not found to be as specific as

the >70% threshold for predicting incomplete bolus transit in symptomatic patients.[17] Similarly, in 351 symptomatic esophageal patients, patients with 50%–70% ineffective swallows had esophageal AET similar to those with <50% ineffective swallows, in contrast to patients with >70% ineffective swallows ($p = 0.048$ across groups).[10] Among patients with 50%–70% ineffective swallows, the absence of contraction reserve on MRS was associated with higher total and upright AET compared to presence of contraction reserve.[24]

7.3 | Supportive testing

Supportive testing for a diagnosis of IEM could include poor bolus transit on impedance or barium esophagram (Very Low GRADE, Conditional Recommendation).[40–42]

Supportive testing for a diagnosis of IEM could include lack of contraction reserve on MRS (Very Low GRADE, Conditional Recommendation).[20]

In patients undergoing HRM with impedance, normal bolus clearance was seen less often in IEM patients (45.5%) compared to normal motility (76.5%, $p < 0.01$), with a modest inverse correlation with dysphagia in IEM patients ($r = -0.37$).[40] Since visual assessment of impedance color contours on HRM may be subjective and inconsistent, novel software tools have been studied to quantify bolus presence by summating pixel impedance volumes as a product of impedance value, pixel time resolution, and spatial resolution, termed esophageal impedance integral (EII).[41] The efficacy of bolus clearance can be described as ratio of bolus presence following peristalsis to that preceding peristalsis, termed the EII ratio,[41] a reproducible metric,[43] that may have a relationship with patient-reported dysphagia when abnormal.[42,44,45] When compared with bolus transit on concurrent barium radiography, EII ratio ≥0.3 correlated with bolus retention.[41] Relationships between EII ratio, DCI, and transition zone defects continue to be studied in predicting abnormal bolus clearance and patient-reported symptoms.[40,42]

In a study of 191 symptomatic patients, those with an inconclusive diagnosis of IEM (50%–70% ineffective swallows) and contraction reserve on MRS had similar esophageal AET compared to patients with normal HRM. In contrast, in inconclusive IEM without contraction reserve, total and upright AET were significantly higher compared to those with contraction reserve. These differences were most marked when upright AET was evaluated ($p \leq 0.02$ for each comparison with normal HRM and inconclusive IEM with contraction reserve).[24] Thus, absence of contraction reserve on MRS could support a diagnosis of IEM when the diagnosis is inconclusive. Presence or absence of contraction reserve has little value in segregating reflux burden when esophageal peristaltic performance is intact.[24]

7.4 | Additional considerations

Despite the frequent association of IEM and abnormal reflux monitoring, IEM is not pathognomonic for the presence of GERD[29] and does not reliably predict transit symptoms or reflux symptoms.[46–48] In fact, as many as 11%–17% of asymptomatic subjects may fulfill CCv3.0 IEM criteria,[5,14,49] by far the most common motor disorder identified in health. A confounder in the diagnosis of IEM is study position. The proportion of healthy volunteers with IEM is higher with upright swallows (23.7%) compared to supine swallows (11.7%, $p = 0.01$).[5] Using CCv4.0 criteria, the incidence of IEM decreased to 10.0% overall among healthy volunteers, 7.1%–8.5% in supine HRM studies, and 5.3%–15.8% in upright studies (p = ns).[5]

Despite prevalence in healthy volunteers, IEM using both CCv3.0 and CCv4.0 criteria does associate with higher AET compared to normal motility in patients with GERD.[10,36] The relationship between hypomotility and reflux disease continues to be evaluated, and peristaltic dysfunction is encountered more often in the context of reflux-related endoscopic changes including Barrett's esophagus.[29,50]

Limited evidence exists suggesting that esophageal peristalsis of even low contraction vigor may be adequate for bolus transit, but breaks in peristaltic integrity are consistently associated with bolus escape.[9,35]

8 | ABSENT CONTRACTILITY

The CCv3.0 criteria for a diagnosis of absent contractility were retained in CCv4.0.

8.1 | Conclusive diagnosis

A conclusive diagnosis for absent contractility requires normal EGJ relaxation (normal median IRP in the supine and upright position) and 100% failed peristalsis (DCI <100 mmHg·s·cm).

Absent contractility is most commonly idiopathic in etiology and is rarely encountered in healthy volunteers (0.4% prevalence among 469 healthy volunteers from around the world).[5] The prevalence among 1081 GERD patients being evaluated for antireflux surgery was 3.2%.[33] As many as 40%–44% of patients with systemic sclerosis have evidence of absent contractility.[51] The finding of absent contractility is not synonymous with systemic sclerosis or collagen vascular disorders, and this pattern should not prompt evaluation for these diagnoses in the absence of other suggestive clinical features.

Absent contractility was associated with extremely high esophageal acid burden (upright AET 17.2% and supine AET 13.5% in one study).[24]

8.2 | Inconclusive diagnosis

In the context of absent contractility, borderline median IRP values, particularly supine median IRP of 10-15 mmHg using the Medtronic system, should prompt consideration of type I achalasia.

In recent years, the fact that achalasia can be diagnosed with median IRP values in the normal range has been increasingly recognized.[52] This is particularly relevant to absent contractility, where the possibility of type 1 achalasia needs to be strongly considered in the presence of consistent symptoms, especially if IRP is >10 mmHg when using the Medtronic system.[53] Although symptom scores for dysphagia (e.g., Eckardt score) can be abnormal in achalasia, these by themselves are not sufficiently reliable to confirm or exclude achalasia. Therefore, alternate testing is important if achalasia remains in the differential diagnosis, especially since the diagnosis of achalasia brings the prospect of LES disruption and symptom improvement into the picture.[54,55]

8.3 | Supportive testing

Supportive testing with TBE with tablet and FLIP should be considered in these cases if dysphagia is the dominant symptom.

Barium radiography is widely available and can be utilized as a complementary test to confirm or rule out achalasia when dysphagia is the dominant symptom in absent contractility.[55] Administration of 8 oz (200–240 ml) of liquid barium in the upright position (TBE) utilizes barium retention (barium height > 5 cm at 1 min and >2 cm at 5 min) to define abnormal barium transit, with sensitivity of 85%–94% and specificity of 71%–86% for diagnosing achalasia.[56] Combining a 13 mm barium pill swallow with TBE increased the diagnostic yield from 80% to 100% in one study.[56] Bolus retention can be evaluated using HRM with impedance following a 200 ml bolus in the upright position, where presence of a water column on impedance topography may provide similar evidence for distal obstruction as TBE.[57]

Functional lumen imaging probe (FLIP) can also be utilized as an adjunctive test to clarify the presence of achalasia when absent contractility is encountered.[54,55,58] In 13 patients with absent contractility presenting as dysphagia and radiologic evidence of achalasia, FLIP demonstrated markedly reduced distensibility index (0.8 mm^2/mmHg) compared to healthy controls (6.3 mm^2/mmHg), which improved significantly following achalasia management (3.5 mm^2/mmHg).[52]

8.4 | Additional considerations

There is no specific management option available for absent contractility, and esophageal peristalsis is not expected to recover. The most significant consequence of absent contractility is GERD, often manifesting with refractory symptoms, high esophageal acid burden on reflux monitoring, and evidence of mucosal injury.[24] Provocative testing with MRS typically does not elicit contraction reserve in absent contractility.[59] Management involves aggressive antisecretory therapy, postural measures, and lifestyle changes to reduce reflux, but partial antireflux surgery is sometimes needed.

9 | STATEMENTS NOT MEETING CCv4 ENDORSEMENT

9.1 | Absent contraction reserve on MRS is consistent with IEM

Even healthy individuals do not always have evidence of contraction reserve, especially if a single MRS maneuver is performed. Contraction reserve was elicited in only 78%–79% of healthy volunteers after a single MRS in two separate studies.[19,60] The presence of contraction reserve is significantly lower in symptomatic patients (50%–62%), and in IEM (65%–69%).[24,60] The optimal number of MRS for a reliable estimation of contraction reserve has been demonstrated to be three attempts.[61] Since a fifth of healthy volunteers do not have contraction reserve, this finding is not always consistent with IEM.

9.2 | Absent contraction reserve on MRS should be required in the definition of IEM

Absent contraction reserve is seen in 35% of patients with CCv4.0 definition of IEM, with no difference in acid burden between those with and without contraction reserve.[24] In patients with 50%–70% ineffective swallows, contraction reserve is absent in 26%, which is similar to that seen in healthy volunteers (21%–22%).[19,24,60] Therefore, even healthy volunteers can have subsets with absent contraction reserve, and this criterion therefore was not considered a requirement for the definition of IEM.

9.3 | Lack of augmentation of DCI on solid test meal may support IEM

STM continues to be studied as a provocative test during HRM in select patients. Contraction reserve during STM consists of DCI augmentation or conversion of IEM to normal motility, and normative data are available.[49] In a validation cohort of patients with reflux symptoms, 35%–40% of patients with IEM had contraction reserve during a solid test meal, but 6% with normal standard manometry demonstrated ineffective swallows and no contraction reserve with STM.[15] Additionally, absence of contraction reserve was also seen in the context of dysphagia in a subset of patients with EGJ outflow obstruction.[15,62] Thus, non-standard swallows during STM make contraction reserve difficult to interpret, even though DCI augmentation could support contraction reserve, and lack of augmentation could be a marker for advanced IEM.[15,27,62] Variations in meal preparation and content, procedure technique, analysis, and requirement of staff time and effort make STM a niche maneuver rather than a routine component of HRM. Therefore, STM findings were not considered a requirement for IEM diagnosis.

10 | CLINICAL CONSIDERATIONS

When esophageal hypomotility is diagnosed, the clinical scenario of the patient being investigated determines the clinical relevance. This is important to recognize, since IEM as it is currently diagnosed can be encountered in asymptomatic healthy individuals.[5] Additionally, observational studies report no difference in proportions of symptoms, including heartburn, regurgitation, dysphagia, chest pain and belching are reported in patients with and without IEM.[34,63] The perception of dysphagia is also imperfect, despite abnormal bolus transit from weak or absent peristalsis.[35,47] In most instances, IEM does not impact quality of life and does not progress over time.[64]

Relevant clinical presentations that may need further distinction within esophageal hypomotility disorders include reflux disease and dysphagia syndromes (Figure 3). Potential implications relate to GERD severity, symptom reporting and decision-making prior to antireflux surgery. Provocative testing with MRS can be useful when IEM is diagnosed in GERD patients, especially prior to antireflux surgery, where absence of contraction reserve can associate with a higher likelihood of post-operative dysphagia.[19,25] While some IEM patients demonstrate improvement or even resolution of peristaltic dysfunction following antireflux surgery, others demonstrate worsening of peristalsis over time, and yet others with normal peristalsis preoperatively develop IEM postoperatively.[23,65] Significant esophageal hypomotility is relative contraindication for magnetic sphincter augmentation (MSA), since contraction vigor is needed to provide propulsive force to distend the MSA device for antegrade transit.[66,67] Severe hypomotility, especially without contraction reserve or with absent contractility in the pre-operative GERD patient, could influence selection of surgical technique, although existing literature using older IEM definitions does not explicitly provide this directive.[65,68–70]

In contrast, dysphagia presentations associated with profound esophageal hypomotility disorders need to be investigated for esophageal outflow obstruction and achalasia spectrum disorders (Figure 4), using RDC, solid swallows, standardized test meal, and TBE, where adequacy of clearance of ingested bolus and symptom reproduction is assessed.[27,56,62,71] FLIP is a complementary technique in this setting.[58] Post-prandial syndromes, especially belching syndromes and regurgitation, can benefit from prolonged HRIM studies that include a standardized test meal with post-prandial monitoring.[72] Appropriate training of HRM operators can provide understanding of clinical relevance so that the operator can adapt the HRM protocol to the clinical scenario and the preliminary diagnosis on standard HRM.

11 | MANAGEMENT

Esophageal hypomotility disorders are difficult to manage, since no pharmacologic intervention reliably restores esophageal smooth muscle contractility or improves symptoms.[73] Therefore, asymptomatic hypomotility disorders in the absence of documented reflux damage do not require specific management. When GERD is identified, typical GERD management recommendations suffice, including dietary and lifestyle changes and antisecretory therapy; this may need to be escalated to antireflux surgery or invasive interventions under certain circumstances.[31,74]

Conventional prokinetic agents (metoclopramide and domperidone) are not beneficial in esophageal hypomotility and do not improve esophageal symptoms. Two 5HT-4 agonists, mosapride and revexepride, have not been demonstrated to improve symptoms in PPI refractory reflux disease in randomized controlled trials,[75–77] although mosapride may facilitate secondary peristalsis induced by rapid air distension in patients with IEM, albeit without improvement in contraction vigor.[78] Prucalopride, another selective 5HT-4 agonist, reduced esophageal acid exposure and accelerated gastric emptying in healthy controls,[79] but patient data are limited to improvement in AET and esophageal symptoms in 4 GERD patients with concurrent constipation.[80] Buspirone, a mixed partial 5HT-1A agonist and dopamine D2 receptor antagonist, was no more effective than placebo in IEM with dysphagia,[81] despite improving esophageal contraction amplitudes in certain scleroderma patients.[82–84] In sum, prokinetics do not have a demonstrable benefit in esophageal hypomotility disorders.

In the absence of specific therapeutic options, alternative and non-pharmacologic options have been studied in esophageal hypomotility disorders. Good swallowing techniques, including cutting food into small pieces, chewing carefully, eating in the upright position, and chasing solids with fluids, are helpful recommendations when dysphagia is the dominant symptom. Psyllium (15 g per day) has been hypothesized to bind nitric oxide contained in food, with decreased heartburn, reduced numbers of reflux episodes, and improved LES resting pressure (potentially from reducing the inhibitory effect of nitric oxide) following psyllium administration in a small open-label study of patients with GERD.[85] However, use in patients with esophageal motor disorders could be problematic and is not recommended. Diaphragmatic breathing has been reported to improve EGJ barrier function and even improve esophageal contraction vigor under limited study circumstances, but long-term effects are unknown.[86,87] Other behavioral approaches including coping strategies, hypnotherapy, cognitive, and behavioral therapy could provide adjunctive value in symptom management.[88] Transcranial direct current stimulation of the brain has been reported to improve esophageal contractility in NERD and functional heartburn in a randomized double-blind sham-controlled study.[89]

12 | FUTURE DIRECTION AND RESEARCH

Esophageal hypomotility disorders are heterogenous, and IEM in particular is encountered in at least 10% of healthy volunteers. This could indicate that the contraction vigor thresholds currently employed for defining ineffective swallows are too high. In fact, the

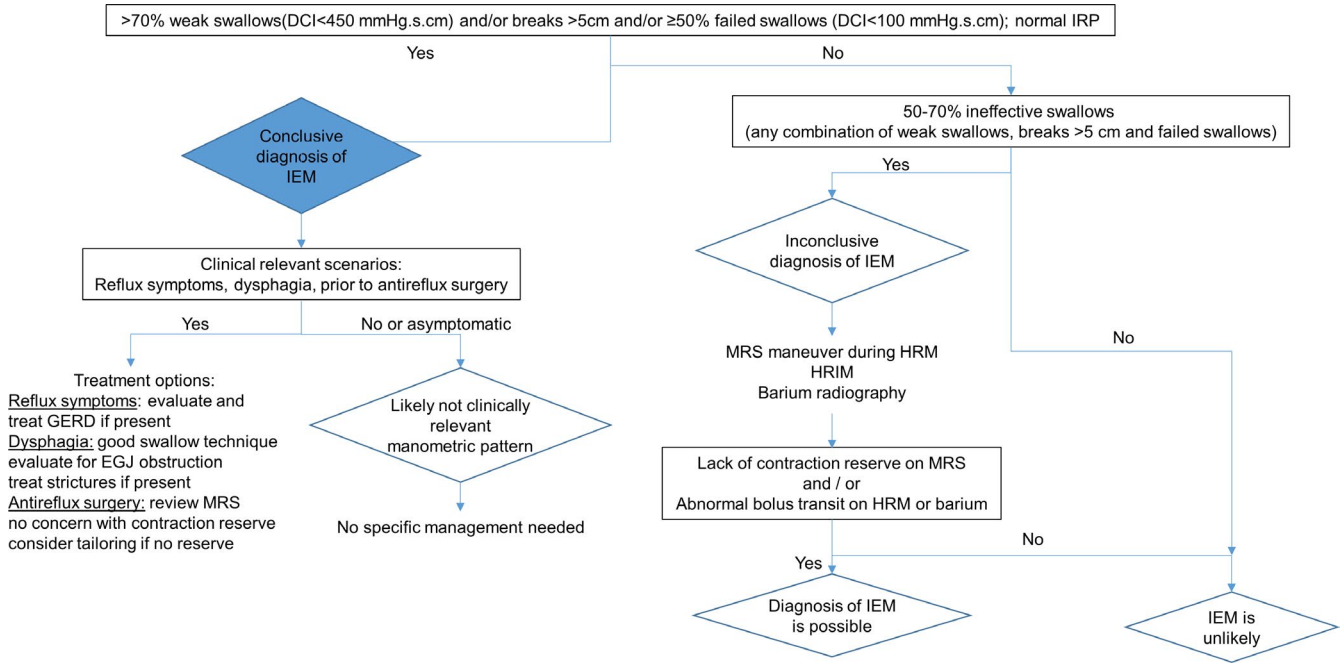

FIGURE 3 Algorithm for the diagnosis and management of ineffective esophageal motility (IEM) using Chicago Classification version 4.0 criteria. DCI, distal contractile integral; EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; HRIM, high-resolution impedance manometry; HRM, high-resolution manometry; IRP, integrated relaxation pressure; MRS, multiple rapid swallows

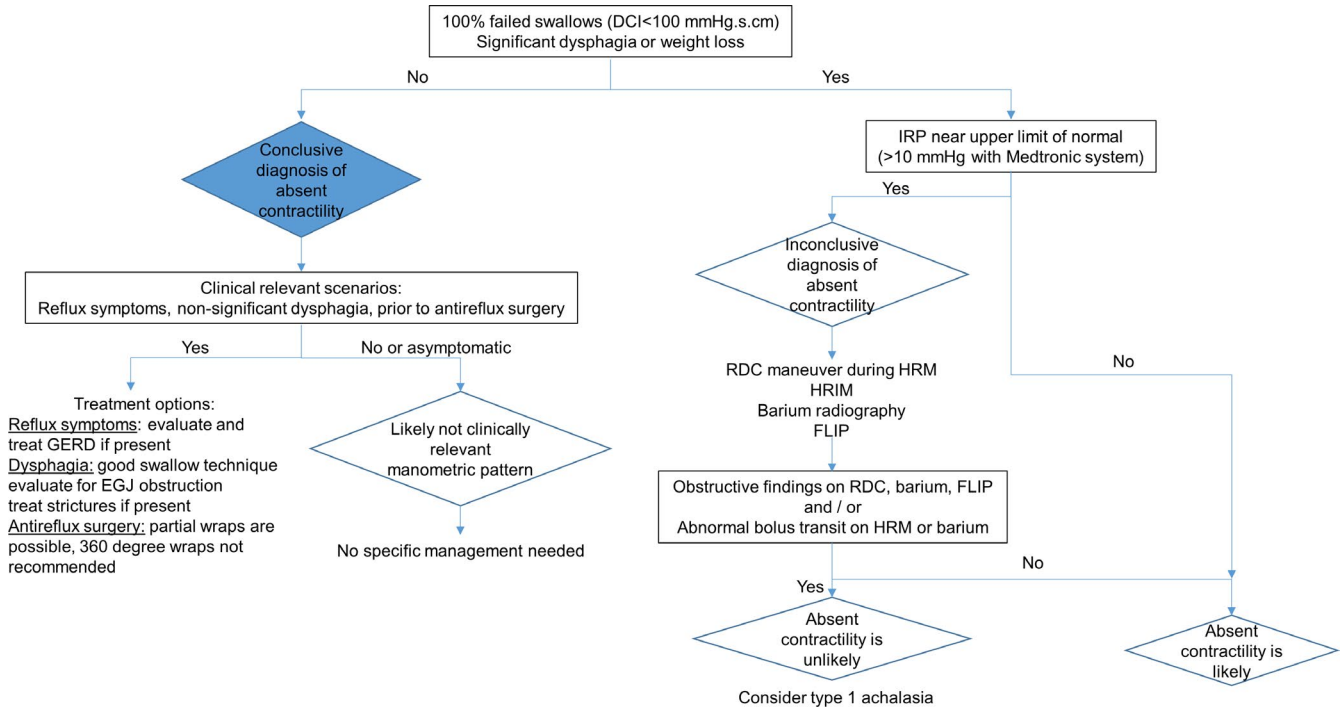

FIGURE 4 Algorithm for the diagnosis and management of absent contractility using Chicago Classification version 4.0 criteria. DCI, distal contractile integral; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; IRP, integrated relaxation pressure; MRS, multiple rapid swallows; RDC, rapid drink challenge

95th percentile DCI value in swallows acquired from 469 healthy volunteers ranged from 200 to 300 mmHg.cm.s, depending on the HRM system utilized, with even lower DCI values and higher proportions of ineffective swallows in the upright position.[5] Future research will need to better define DCI thresholds above which bolus transit consistently occurs, as the currently utilized thresholds are extrapolated from contraction amplitudes measured using conventional manometry.

The use of stationary impedance with HRM (high-resolution impedance manometry) needs to be further studied in defining bolus transit concurrent with peristaltic patterns. Newer interpretation metrics and paradigms, using EII, bolus flow time, and other yet to be developed novel metrics will need to be evaluated to better quantify bolus transit. Relationship of symptoms to motor patterns will need further study, using these newer metrics. Although more prokinetic agents are becoming available, scenarios where these agents impact patient symptoms or disease states like GERD need to be better evaluated, and newer prokinetic agents with demonstrable peristaltic and symptom benefits need to be developed. Outcome of antireflux surgery in the context of hypomotility disorders needs further study, in particular, whether tailoring of fundoplication is necessary in patients with IEM with and without contraction reserve.

The pathophysiology and control mechanisms underlying esophageal hypomotility disorders, particularly IEM, are incompletely understood. Central and peripheral triggers continue to be studied and could pave the way for novel therapeutic targets and management modalities.

The new criteria for definition of IEM in particular have potential to further refine the motor disorder, and efforts to better relate the manometric pattern with symptoms, management, and clinical outcome will benefit the field. Ultimately, however, hypomotility disorders have limited sinister consequences, and observational studies of the natural history of these disorders could provide further reassurance that these disorders are clinical curiosities without significant impact in quality of life in many instances, as demonstrated by some existing studies.

DISCLOSURES

CPG: Medtronic, Diversatek, Ironwood, Isothrive, Quintiles (consulting); FZ: Reckitt Benckiser (consulting); SB: no disclosures; DC: no disclosures; ECA: Medtronic (consulting and speakers bureau); AL: no disclosures; DP: Medtronic, Sanofi (consulting), Vifor (travel grant); RY: Medtronic, Diversatek, Ironwood (institutional consulting), Phathom Pharmaceuticals (consulting), Ironwood (research grant), RJS Mediagnostix (advisory board with stock options); RP: no disclosures; JP: Consultant: Medtronic, Ironwood Pharmaceuticals, Diversatek; Research support: Ironwood Pharmaceuticals, Takeda; Advisory Board: Medtronic, Diversatek; Stock Options: Crospon Inc.

AUTHOR CONTRIBUTIONS

All authors contributed to the content of the manuscript, and reviewed, edited, and approved the final draft.

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