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Dysphagia:

Novel and Emerging Diagnostic Modalities

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INTRODUCTION

Advances in diagnostic testing for esophageal motility disorders have been substantial over the past 10 to 20 years. The advent of high-resolution manometry (HRM) and esophageal pressure topography (EPT) in the 1990s provided a method to improve depiction of esophageal motor function over conventional line tracing manometry and facilitated organized classification of esophageal motility disorders via the Chicago Classification (CC).[1–3] A novel tool and approach with functional luminal imaging probe (FLIP) panometry, as well as application of barium esophagram, have both helped clinicians to improve diagnostic capabilities. The purpose of this review article is to discuss the current and emerging technologies in the area of esophageal motility and to discuss the authors' approach to diagnosing and managing esophageal motility disorders.

APPROACH TO DYSPHAGIA AND DIAGNOSIS OF ESOPHAGEAL MOTILITY DISORDERS

The clinical evaluation of dysphagia begins with the clinical history with the initial distinction typically related to differentiating between oropharyngeal and esophageal dysphagia. When oropharyngeal dysphagia is suspected, video fluoroscopic swallow examination and evaluation by speech therapy may be considered. With dysphagia that is esophageal in origin, the clinical history for dysphagia may suggest mechanical or motor causes (eg, dysphagia to solids vs liquids), although ultimately that determination will be yielded through objective testing. Thus, the clinical history related to a possible esophageal motility disorder seeks to assess for potential secondary causes of esophageal motor dysfunction, such as previous foregut surgery, as these are essential to incorporate into a subsequent clinical impression. The association of chronic opioid use and esophageal

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DISCLOSURE

Northwestern University holds shared intellectual property rights and ownership surrounding FLIP Panometry systems, methods, and apparatus with Medtronic Inc. D.A. Carlson: Medtronic (Speaking. Consulting); A.J. Krause: None.

motor dysfunction also garnered recent interest, because of an association with elevated esophagogastric junction (EGJ) outflow pressures on HRM and even spastic achalasia.[4–6]

The initial objective evaluation for esophageal dysphagia is typically endoscopy. A careful endoscopic evaluation is essential to evaluate for mechanical causes of obstruction, including strictures, rings, eosinophilic esophagitis (EoE), advanced erosive esophagitis, hiatal hernias, and, of course (although a vast minority of cases), tumors. In the absence of mechanical obstruction or other alternative cause for dysphagia, an evaluation for esophageal motility disorders should be then pursued.

HIGH-RESOLUTION MANOMETRY AND THE CHICAGO CLASSIFICATION

HRM uses a solid-state catheter assembly with closely spaced pressure sensors (typically 1-cm spacing intervals) that are positioned to traverse the entire length of the esophagus. Software interpolation of this pressure data to EPT allows visualization of esophageal motor function along a space-time-pressure continuum. Furthermore, EPT metrics were developed to quantify components of esophageal motor function, such as deglutitive lower-esophageal sphincter (LES) relaxation via the integrated relaxation pressure (IRP) and peristaltic vigor via the distal contractile integral (DCI).[7,8] These EPT metrics, as well as recognition of pressurization patterns on EPT, facilitated development of a hierarchical classification scheme of esophageal motility disorders: the CC.[2] The CC provides a standard terminology for description of esophageal motility disorders and is used around the world. HRM and the CC provided a method to improve accuracy of interpretation and diagnostic yield for esophageal motility disorders over conventional line tracings.[9,10] The CC was initially published in 2009 and has evolved to reflect advances in the application of HRM through intermittent updates, including the most up-to-date version 4.0 (CCv4.0) published in 2021.[3,11–13] This recent update involved application of RAND methodology to reflect recommendations developed over a 2-year process by the International HRM Working Group, as well as application of the Grading of Recommendations Assessment, Development, and Evaluation process.[3] The working group comprised 52 members selected by 6 international motility societies from 20 different countries.

There were several major updates reflected in the CCv4.0 as compared with the earlier iterations.[3,11,14] One related to standardization of the HRM test protocol, which involved expansion of the protocol and application of complementary provocative maneuvers (Table 1). In addition, an important concept sought with CCv4.0 was to identify conclusive and clinically relevant esophageal motility disorders, as compared with inconclusive HRM motor patterns. This was based on the recognition that some manometric patterns do not always equate to a clinical disease, that is, are inconclusive. This most notably led to modification to criteria for EGJ outflow obstruction (EGJOO) and ineffective esophageal motility (IEM) and sought to identify HRM findings with increased relevance for these classifications. The HRM pattern of EGJOO, however, was recommended to always be considered an inconclusive *manometric* diagnosis until confirmed by additional complementary testing with barium esophagram or FLIP. Application of clinical (symptom-based) criteria was also applied to the EGJOO classification, as well as to distal esophageal spasm (DES) and hypercontractile esophagus. This was based on recognition that these manometric patterns

may not uniformly equate to a clinical disease when they are not associated with noncardiac chest pain and/or dysphagia.

Of note, the diagnosis of primary esophageal motility disorders, and thus the direct application of CCv4.0, is intended for patients with normal foregut anatomy (eg, do not have a large hiatal hernia or paraesophageal hernia) and who have not undergone any previous surgical or invasive foregut interventions.[3] This naturally stipulates that the HRM is interpreted in the context of endoscopic and/or esophagram findings.[3] If manometry is performed in the context of previous foregut surgery or a mechanical obstruction/abnormal anatomy, the CC metrics and interpretation may be used as a standard descriptive method, while recognizing the potential for secondary motor findings.

MANOMETRY TEST PROTOCOL

Previous versions of the CC were based on the cumulative outcome of 10 swallows of 5-mL liquid performed in a single patient position (typically supine).[2,11,14] However, value in performing HRM in 2 patient positions was observed, particularly via the potential to relieve manometric pressure artifact (eg, a false-positive IRP elevation) at the EGJ.[15–17] In addition, provocative HRM maneuvers, such as multiple rapid swallows (MRS), rapid drink challenge (RDC), solid test swallows, solid test meal (STM), pharmacologic challenges, and postprandial monitoring periods, were also reported to complement standard test swallows and potentially increase diagnostic yield of HRM (see Table 1).[17–23] Thus, CCv4.0 provided recommendations for a standard HRM protocol, as well as incorporation of complementary maneuvers.

The standard HRM protocol, as discussed in CCv4.0, begins with the patient in a supine position. After a catheter is placed, 60 seconds of time is allotted to ensure a normalization period. A baseline of 30 seconds is captured in order to identify the upper-esophageal sphincter, LES, respiratory inversion point, and basal EGJ pressure.[3] Next, ten 5-mL wet swallows are completed in the primary position (typically supine) and five 5-mL wet swallows are completed in the secondary (typically upright) position. At least 1 MRS and 1 RDC are also recommended (see Table 1).[3]

If the above testing is inconclusive, additional maneuvers can be considered (see Table 1). Solid test swallows and STM can be used to further evaluate the HRM diagnosis of EGJOO (see Table 1).[3,20,21] In patients in whom there is concern for a diagnosis of achalasia (but with an inconclusive HRM) or opioid esophagus, a pharmacologic provocation can be performed.[3,17] Monitoring after a meal (a postprandial study) can also be applied to aid identification of patients suspected to have rumination and/or belching disorder.[23–25] Although if the results of HRM are ambiguous, which in particular includes any case with an HRM classification of EGJOO, a timed barium esophagram (TBE) with a barium tablet swallow and/or FLIP can be used.[3,26,27]

DIAGNOSTIC CRITERIA FOR ESOPHAGEAL MOTILITY DISORDERS

HRM provides a framework for diagnosing disorders of esophageal motility. The CCv4.0, similar to previous iterations of the CC, splits the possible diagnoses into major categories

of esophageal dysfunction as disorders of EGJ function (including type I, II, and III achalasia and EGJOO; Fig. 1) and disorders of peristalsis (including absent contractility, DES, hypercontractile esophagus, and IEM; Fig. 2).

Also of note is that application of the HRM metric values varies related to bolus consistency and volume, patient position, test maneuver, and HRM assembly manufacturer (Table 2). Thus, application of these values is imperative for interpretation of the HRM study.

Disorders of EGJ function are categorized by an elevated median IRP, either in the supine or in the upright positions (see Fig. 1).

Achalasia

Achalasia represents the prototypical esophageal motility disorder and as such carries effective, targeted treatment options.[28] Achalasia is identified on manometry by elevated LES relaxation pressures and absence of peristalsis. Furthermore, achalasia can be subclassified based on pressurization pattern (type I vs type II) or presence of spastic contraction (type III) (see Fig. 1). The achalasia subtypes carry clinical relevance related to prognosis to treatment, such that type II achalasia has the best treatment outcomes.[29–31] More importantly, the achalasia subtypes direct management decisions in achalasia such that patients with type III achalasia may have better clinical outcomes if preferentially treated with surgical LES myotomy than with pneumatic dilation.[30]

Also worth noting is that patients may have achalasia, but without elevated IRP on HRM. Thus, in these inconclusive cases in which achalasia is clinically suspected, particularly if the IRP values are at the upper limits of normal, complementary evaluation with TBE or FLIP can help confirm an achalasia diagnosis.[3,32]

Esophagogastric Junction Outflow Obstruction

The HRM classification of EGJOO is reached when the IRP is elevated, but peristalsis is present such that criteria for an achalasia subtype are not met. The EGJOO classification was specifically recognized as a limitation in previous versions of the CC related to heterogeneity of clinical diagnosis that could be represented within this HRM pattern. For example, EGJOO on HRM could reflect a variant of achalasia, but could also be related to hiatal hernia, extrinsic esophageal compression, or even artifactual elevation of IRP (in the setting of otherwise normal esophageal motility).[15–17,33,34] Studies suggested that only a minority (<25%) of patients with this HRM pattern represented a primary esophageal motor disorder akin to achalasia and that most patients would instead improve from conservative management alone.[33,34] Thus, the clinical relevance of this HRM pattern was often uncertain.

As a result of this, the classification of EGJOO was modified in CCv4.0 to require that if peristalsis was present such that a conclusive diagnosis of achalasia was not achieved, then a manometric classification of EGJOO required an elevated median IRP in *both* supine and upright swallows, in addition to the presence of elevated intrabolus pressure with supine wet swallows.[3] An isolated IRP elevation (ie, if IRP normalizes in the second position) likely reflects that the initial IRP elevation was related to pressure artifact, as these isolated IRP

elevations were observed to rarely be associated with retention on barium esophagram, that is, rarely clinically significant.[16] The abnormal bolus pressurization provided an additional feature to support the presence of an EGJOO. The HRM classification of EGJOO also required the presence of a relevant symptom (dysphagia or chest pain) to support it as a clinically relevant HRM finding. It was also recommended that the EGJOO classification also be described relative to the pattern of esophageal contractility (eg, spastic or ineffective or normal peristalsis) to further characterize the esophageal motor function. However, the ultimate recommendation from the CCv4.0 was that manometric EGJOO should always be considered an inconclusive clinical diagnosis, and that additional complementary testing with TBE or FLIP be applied to confirm the diagnosis. This is particularly essential before consideration for invasive achalasia-type treatments.

Application of provocative HRM maneuvers may also be useful to complement the overall HRM impression to aid identification of EGJOO (see Table 1). Having an elevated IRP greater than 12 mm Hg (Medtronic assembly) during the MRS and RDC in patients with an elevated IRP in both the supine and the upright positions is more likely to be associated with an abnormal esophagram with either retention on the TBE or barium tablet delay, and consequently, a diagnosis of clinically relevant outflow obstruction.[35] In addition, an elevated IRP > 12 mm Hg (Medtronic software) plus panesophageal pressurization during the RDC may be more suggestive of EGJOO.[35]

Disorders of Peristalsis

When EGJ outflow is normal, the CC applies a frequency of swallow types from the primary position of test swallows to seek disorders of peristalsis. The criteria for absent contractility have not changed in the current iteration of the CC (see Fig. 2).[3] DES and hypercontractile esophagus in CCv4.0 have now been classified as clinically relevant in patients with manometric findings of DES (see Fig. 2) as well as symptoms of dysphagia and/or noncardiac chest pain.[3] However, these diagnoses can also be patterns of uncertain clinical significance, such as in association with gastroesophageal reflux disease,[36] secondary manifestation of obstruction,[37] and even potential (albeit) rare overlap with healthy controls.[38] With regards to hypercontractile esophagus, DES and/or achalasia criteria must not be met, and a mechanical obstruction must be ruled out.[3] In addition, achalasia should be considered, particularly if the IRP is near upper limit of normal.[32] Finally, IEM, previously considered a “minor disorder” of peristalsis, now has more rigorous pathologic criteria for diagnosis and includes fragmented peristalsis.[3] This reduced overlap with healthy controls and thus sought to reflect a more clinically relevant phenotype of esophageal hypomotility. Lack of contractile reserve on MRS can be used to further support a diagnosis of IEM (see Table 1).[3,39]

IMPEDANCE MANOMETRY

Intraluminal impedance measurements relate to the contents of the esophagus such that impedance decreases with intraluminal liquid and increases with intraluminal air. Thus, impedance-manometry or high-resolution impedance manometry (HRIM) provides methods to objectively assess bolus transit, bolus clearance, intrabolus pressure, and

relationships between esophageal pressure and bolus flow.[40–43] However, despite the additional information provided with impedance manometry, the clinical utility remains a topic of debate, and as such, impedance was not included in CCv4.0.

With impedance-manometry, bolus transit and clearance can be evaluated in a dichotomy (complete or incomplete) with previous studies demonstrating abnormal bolus transit among patients with esophageal motility disorders, such as IEM and achalasia.[40,44] An innovative methodology for HRIM interpretation was also developed to objectively measure components of bolus flow timing, bolus retention, pressurization, and luminal distension using a pressure-flow analysis paradigm with demonstrated utility in distinguishing between healthy controls and patient cohorts, including postfundoplication dysphagia and nonobstructive dysphagia.[41,45,46] Additional novel HRIM metrics of the bolus flow time and esophageal impedance integral quantify trans-EGJ bolus flow and esophageal retention, respectively; these metrics correlated with symptom scores and clinical outcomes in patients with achalasia and major motor disorders as well as with symptom scores in patients without major motor disorders.[42,43,47,48] The impedance bolus height, another HRIM metric, quantifies esophageal retention after a 200-mL rapid liquid drink in an upright posture by measuring the height of the residual fluid column after 5 minutes, analogous to a timed-barium esophagram.[49] HRIM can also be applied to a postprandial testing protocol to objectively detect behavioral disorders rumination syndrome and supragastric belching, as both rumination events and supragastric belches have an objective appearance on HRIM.[23–25] Thus, although additional clinical study remains needed to further demonstrate the clinical utility of impedance manometry, this technology also holds potential for diagnostic advances in esophageal disorders.

BARIUM ESOPHAGRAM

Barium esophagram facilitates depiction of esophageal anatomic morphology in addition to evaluating esophageal function. The functional assessment can be objectified by application of standard testing protocols, such as the TBE and use of a standardized solid bolus (eg, 12- to 13-mm barium tablet). The TBE protocol typically involves ingestion of 200 to 236 cc of thin barium with images taken at 1 and 5 minutes after ingestion.[50–53] Esophageal retention can then be quantified as the barium column height superior to the EGJ. TBE carries clinical value for evaluation of treatment outcomes in achalasia,[51,53] although also can be a useful complementary test when assessing patients with dysphagia. TBE can be particularly useful in patients in which an initial evaluation with endoscopy and HRM (and/or FLIP) is inconclusive; the HRM pattern of EGJOO is the prime example.[3,27] TBE thresholds for abnormality were proposed as column height greater than 5 cm at 1 minute (with sensitivity and specificity of 94% and 71%, respectively) and greater than 2 cm at 5 minutes (with sensitivity and specificity of 85% and 86%, respectively) to identify patients with untreated achalasia from nonachalasia.[52] Adding the barium tablet retention increased the accuracy of the test.[52]

FUNCTIONAL LUMINAL IMAGING PROBE

The FLIP uses impedance planimetry technology to measure esophageal luminal dimensions (cross-sectional area ~ diameter) and esophageal distensibility (ie, the dimension/pressure relationship) in response to controlled, volumetric distension. The FLIP study is typically performed during sedated endoscopy. The FLIP is commercially available (Medtronic, Inc, Shoreview, MN, USA) in 2 different sizes: 8 cm or 16 cm. Although the 8-cm FLIP can evaluate EGJ distensibility, the 16-cm FLIP provides simultaneous evaluation of the distal esophageal body and EGJ. Furthermore, by displaying the esophageal diameter changes along a space-time continuum with associated pressure using the FLIP panometry approach, EGJ opening mechanics, esophageal body distensibility, and the contractile response to distension, that is, secondary peristalsis, can all be assessed.[54,55]

Utilization of Functional Luminal Imaging Probe Panometry

As FLIP is used at the time of sedated endoscopy, it can be applied during the initial endoscopy for esophageal symptoms if the endoscopic examination is negative or suggestive of an esophageal motility disorder, thus when an evaluation of esophageal motility is warranted. Alternatively, FLIP with endoscopy may also be considered if an initial evaluation with HRM (or TBE) is inconclusive, and thus additional complementary testing is necessary. Other applications of FLIP may also be considered, such as objective evaluation of luminal diameter and distensibility of the esophageal body and/or strictures, such as in EoE or monitoring at the time of or after therapies, such as in achalasia.[56–60]

Functional Luminal Imaging Probe Study Protocol

Variations in FLIP study protocols have been reported, and thus, efforts are ongoing to standardize the FLIP study protocol (Table 3).[61] Although the FLIP study protocol varies slightly whether using the 8- or 16-cm FLIP balloon, both sizes involve maintenance of the adequate positioning of the FLIP relative to the EGJ based on visualization of the EGJ "waist" throughout the duration of the study protocol (Fig. 3) and incremental stepwise filling of the FLIP balloon. Real-time interpretation of the FLIP study is possible and is displayed either solely as the instantaneous FLIP "hourglass" with the FLIP 1.0 display or as FLIP panometry with the FLIP 2.0 display (see Fig. 3; Figs. 4 and 5). In addition, distensibility of the *proximal* esophageal body can also be assessed by, after emptying the FLIP, withdrawing the catheter until the balloon is positioned just below the upper-esophageal sphincter, which may be useful in EoE (see Fig. 5).[55]

It can also be worthwhile to archive the FLIP study data for postprocedural review. This can be accomplished through the FLIP system (which creates a TXT file) or via an additional recorder of the real-time FLIP panometry. The customized program that the authors have used for previous research reports uses the TXT files and is available at http://www.wklytics.com/nmgi.[62,63]

Interpretation and Application of Functional Luminal Imaging Probe Panometry

Esophagogastric junction opening—The evaluation of EGJ distensibility on FLIP panometry uses the metric of EGJ-distensibility index (DI), that is calculated as the EGJ-

cross-sectional area divided by pressure.[64] The maximum EGJ diameter (ie, the greatest diameter achieved at the EGJ) also provides a useful assessment and can complement the EGJ-DI. The authors observed that with the 16-cm FLIP, the EGJ-DI obtained during the 60-mL fill volume and the maximum EGJ-diameter achieved during the 60- to 70-mL fill volume appeared to provide the most reliable performance for EGJ opening evaluation.[55,63] These fill volumes produced a similar degree of FLIP bag filling (and thus similar distensive stimuli) as the 40- to 50-mL fill volumes with the 8-cm FLIP.

The approach to analyze the EGJ opening using FLIP involves first assessing for whether antegrade contractions are occurring, as this impacts the areas at which EGJ opening measurement is made (see Fig. 3). Areas at the EGJ that are affected by *dry catheter artifact*, which is a measurement artifact that impacts diameter measurement when occlusion of the FLIP balloon disrupts the electrical current used for the impedance planimetry technology, need to be recognized (see Fig. 4).[62] Because of the artifact, these areas should be excluded from measurement of the EGJ opening. Analysis can instead include other areas of the FLIP study in which the dry catheter artifact does not occur: this may be during a nonoccluding contraction that may occur later during the same fill volume; immediately before or after occlusion occurs related to the antegrade contraction; or at a higher fill volume (eg, 70 mL) during which occluding contractions are less likely to occur. Also of note is that the EGJ-DI value should not be applied if the associated intrabag pressure is less than 15 mm Hg (and be interpreted somewhat cautiously if the pressure is <20–25 mm Hg), as applying low values to the dividend of the calculation can create a misleadingly elevated EGJ-DI value.

Normal values (ie, those based on testing of asymptomatic volunteers) based on study with the 16-cm FLIP included a median (5–95th) EGJ-DI (60 mL) of 5.8 (3.2–8.4) mm^2/mm Hg and maximum EGJ diameter (60–70 mL) of 20.4 (16.7–21.9) mm.[65] EGJ opening parameters are reduced in esophageal motor disorders of EGJ outflow, such as achalasia; that is, FLIP metrics of EGJ opening are inversely correlated with EGJ pressure measures on HRM.

Although previous thresholds have been proposed,[61,63] the authors recently proposed and validated an updated approach for assessment of EGJ opening with FLIP based on subsequent evaluation of asymptomatic volunteers and patients with achalasia and normal motility on HRM.[55,62,66] With this approach, 2 parameters, the EGJ-DI at the 60-mL fill volume and the maximum EGJ diameter achieved during the 60- to 70-mL fill volumes (based on 16-cm FLIP) were jointly applied: *reduced EGJ opening* (REO) is defined by EGJ-DI less than 2.0 mm^2/mm Hg and a maximum EGJ diameter less than 12 mm. Borderline EGJ opening (BEO) was defined by an EGJ-DI less than 2.0 mm^2/mm Hg or a maximum EGJ diameter less than 16 mm (but not REO). Normal EGJ opening (NEO) was defined by an EGJ-DI ≥2.0 mm^2/mm Hg and ≥16 mm. This provided high degrees of certainty for pathology with REO and normality with NEO to improve the application of these findings. This was demonstrated in a validation study of this approach: 94% (218/233 patients) with REO on FLIP panometry had a conclusive disorder of EGJOO based on CCv4.0 (ie, achalasia subtypes I, II, or III; or EGJOO with a confirmatory abnormal TBE), whereas 96% (138/144 patients) with NEO on FLIP panometry had normal EGJ outflow per CCv4.0 (ie, normal supine and upright IRP).[65] Of 466 patients, 89 patients (19%) had

a BEO classification and would be recommended to undergo additional complementary evaluation.

Contractile response to distension—The esophageal contractile response to distension, that is, evaluation of secondary peristalsis in response to sustained esophageal distension, is performed during the 50- to 70-mL fill volumes of the 16-cm FLIP study protocol. Unique patterns of this esophageal response occur and are amenable to pattern recognition (see Fig. 4). The normal esophageal response to distension that is observed in 90% of healthy asymptomatic volunteers involves antegrade contractions that occur at a regular repetitive rate: repetitive antegrade contractions (RACs). The normal contractile response pattern is further characterized by the RAC Rule-of-6s.[55,67,68] The classification scheme for the FLIP panometry patterns of the contractile response to distension was recently validated based on demonstration of shared features with primary peristaltic function/dysfunction on HRM.[69]

Evaluation of esophageal motility—Esophageal motility can be assessed and classified with FLIP panometry by application of EGJ opening and the contractile response pattern.[61,63,70]

An important distinction to note is that although similar and shared features are observed in esophageal motor function assessed with FLIP panometry and HRM, these 2 tests evaluate different components of esophageal function. Differences in test outcomes may reflect differences in esophageal function between the esophageal response to swallows (HRM) and the esophageal response to distension (FLIP panometry). This was also previously demonstrated with a difference in primary and secondary peristalsis triggered when evaluated with esophageal manometry.[71,72]

The initial study describing this approach demonstrated that application of a hierarchical classification scheme to evaluate esophageal motility with FLIP panometry (akin to the approach of the CC to HRM) demonstrated that FLIP panometry could accurately evaluate esophageal motility, particularly with detection of achalasia: 70/70 included achalasia patients had an abnormal FLIP panometry study.[63] Subsequent studies have provided additional support to the finding that patients with achalasia will consistently have abnormal EGJ opening and an abnormal contractile response to distension on FLIP panometry.[66,67] In addition, FLIP also was useful to confirm an achalasia diagnosis in patients in which achalasia was strongly suspected based on clinical presentation and abnormal esophagram, but that had normal IRP on HRM.[32] Finally, application of FLIP panometry output to a machine-learning algorithm was able to detect nonspastic (HRM subtype I or II achalasia) from spastic (HRM type III achalasia) with 78% to 90% accuracy.[73]

Another scenario in which FLIP panometry was useful to clarify equivocal esophageal motility evaluations was with the EGJOO classification on HRM.[26,63] A study focused on patients with the EGJOO classification on HRM demonstrated that a normal FLIP panometry study among the HRM-EGJOO cohort was associated with normal esophageal clearance on esophagram and symptom improvement with conservative management.[26] Furthermore, patients with HRM-EGJOO and EGJ-DI less than 2.0 mm^2/mm Hg on FLIP

had a higher likelihood of abnormal retention on esophagram and could potentially benefit from LES-targeted treatments.

The implications of a normal FLIP panometry to exclude a major esophageal motor disorder were further described among a cohort of 111 consecutive patients who had also undergone HRM.[68] Of these patients, 70% had normal esophageal motility, and the remainder of the HRM findings were generally considered false positive or equivocal; none had achalasia. This study defined a normal FLIP panometry by an EGJ-DI greater than 3.0 mm^2/mm Hg, lack of repetitive retrograde contractions, and contractile response pattern meeting the RAC Rule-of-6s.[68] In addition, although most patients with normal motility on HRM also had normal findings on FLIP panometry, it should be noted that abnormalities can occur.[62] In a retrospective study of 164 patients with normal esophageal motility on HRM completing FLIP, 27% were found to have abnormal EGJ distensibility, 23% had an abnormal response to distension, and 7% had sustained LES contraction, a pattern during FLIP distension whereby contraction of the LES occurs.[62] However, among the 68 patients who also had undergone an esophagram, abnormal EGJ distensibility was associated with barium retention.[62] Ultimately, a need for future studies to determine the potential for response to targeted therapy was noted.

Overall, FLIP panometry is a valid and useful diagnostic tool for independent and complementary evaluation of esophageal motility at the time of sedated endoscopy. In some scenarios, FLIP panometry could eliminate the need for HRM, for example, a normal FLIP panometry study given the low probability for a major esophageal motor disorder.[68] FLIP panometry can also effectively independently identify achalasia and thus could be sufficient to diagnosis achalasia without HRM, particularly if other clinical information is supportive of the diagnosis (eg, TBE). In other scenarios, FLIP panometry findings may be abnormal, but require clinical correlation with TBE or HRM to clarify (eg, a spastic-reactive contractile response pattern or BEO). Similarly, when HRM findings are inconclusive, application of FLIP panometry can be beneficial to clarify the clinical impression.[3,26,32]

Distensibility of esophageal body—The distensibility plateau, which represents a fixed diameter despite increase in distensive pressure, has been used for evaluation of the esophageal body with FLIP (see Fig. 5).[56,74,75] Compliance measures to reflect change in volume relative to pressure have also been applied.[56,76,77] Although these metrics were generated for research purposes via postprocedural analytical data plots, the distensibility plateau of the esophageal body can be estimated on the real-time FLIP panometry by evaluating the esophageal body diameters at the greatest fill volumes. Normal values of distensibility plateau are ≥18 mm at both the distal and the proximal esophageal body.[55]

A previous study evaluating the clinical application of FLIP in EoE demonstrated that reduced distensibility plateau was associated with risk for food impaction (distensibility plateau <17 mm, in particular) and requirement of therapeutic dilation.[57] In addition, improvement in distensibility plateau occurred in response to dietary or medial EoE therapy, and improvement in distensibility plateau was a stronger indicator of symptomatic improvement than mucosal eosinophil counts.[78] Thus, FLIP provides a role to objectively monitor therapy in EoE.

SUMMARY

Ongoing advances in esophageal motility testing are expected as technologies and approaches evolve with ongoing experience to better categorize patients with motility disorders. HRM and EPT combined with the CCv4.0 provide the cornerstone for the diagnosis of esophageal motility disorders. The most recent updates in the CCv4.0 have focused on standardization of the HRM protocol and have refined the diagnosis of clinically relevant esophageal motility disorders. When approaching a patient with esophageal motility disorders, the history is critical, and initial testing typically includes endoscopy to rule out any mechanical causes of obstruction. Apart from the standardized HRM protocol, there are numerous additional testing strategies, such as MRS, RDC, solid test swallow, STM, pharmacologic provocation, impedance, TBE, and FLIP, that can aid clinicians in the diagnosis of esophageal motility disorders. As the field continues to develop and expand, it is hoped that the diagnostic algorithm can be further standardized and simplified and ultimately can direct targeted, effective treatment strategies for patients suffering from esophageal disorders.

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KEY POINTS

- The Chicago Classification version 4.0 represents the state-of-the art diagnostic algorithm for esophageal motility disorders with high-resolution manometry (HRM).
- Provocative HRM maneuvers, including multiple rapid swallows, rapid drink challenge, solid test swallow, solid test meal, pharmacologic provocation, and impedance, can help complement the standard HRM interpretation.
- Timed barium esophagram provides a useful complementary esophageal motility evaluation, especially if initial testing is inconclusive.
- Functional luminal imaging probe panometry evaluates the esophageal response to distension and is a promising modality for the evaluation of esophageal distensibility and motility.

CLINICS CARE POINTS

- Initial objective evaluation for esophageal dysphagia is generally endoscopy to rule out mechanical causes of obstruction.
- If endoscopy is unrevealing for an objective diagnosis for a cause of dysphagia, esophageal motility testing with high-resolution manometry (HRM) or functional luminal imaging probe (FLIP) should be considered.
- The Chicago Classification provides the current diagnostic algorithm for esophageal motility disorders and highlights complementary testing strategies for further characterizing these disorders.
- Complementary testing strategies include the MRS, RDC, solid test swallow, STM, pharmacologic provocation, impedance, TBE, and FLIP panometry.
- When HRM findings are inconclusive, the utilization of FLIP panometry can help to clarify the clinical diagnosis.
- FLIP panometry is a useful diagnostic test that can be completed during a sedated endoscopy and could eliminate the need for HRM if normal.

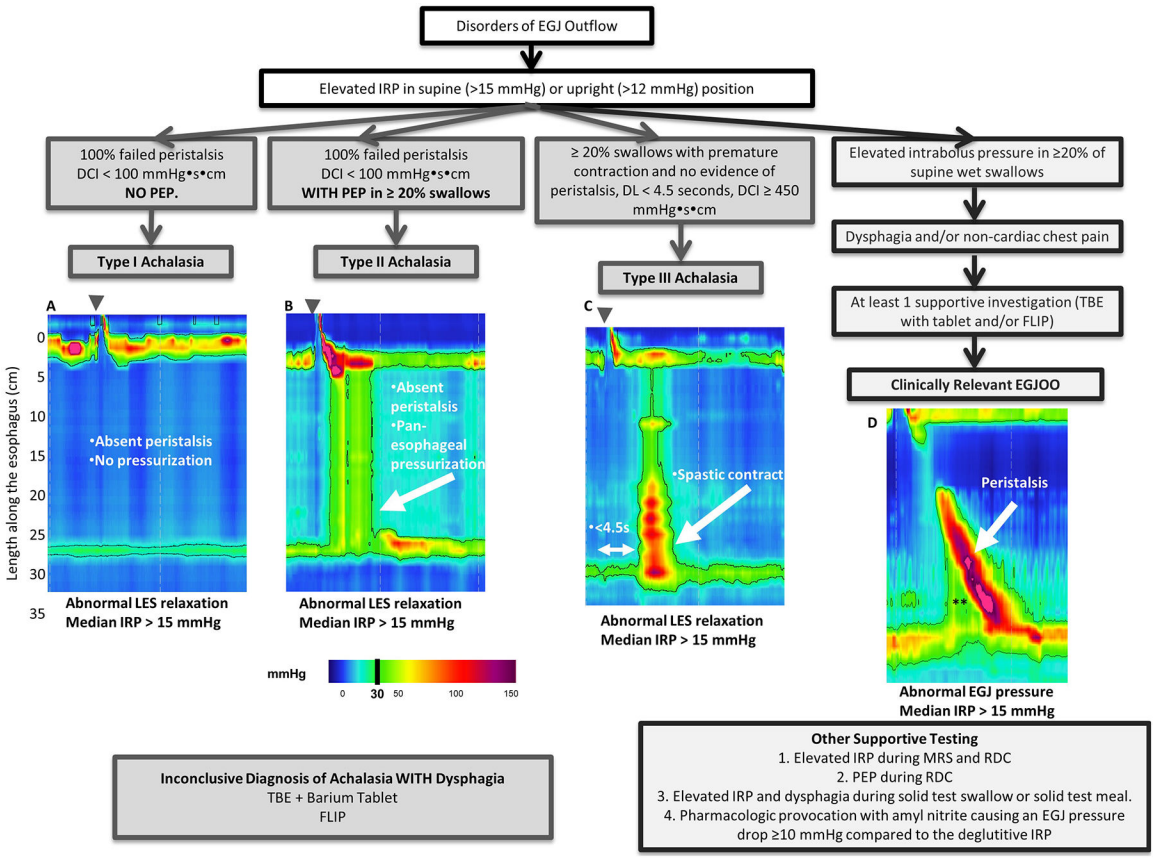

Fig. 1.

CCv4.0 disorders of EGJ outflow. The disorders of EGJOO. (*A*) Type I achalasia on HRM. (*B*) Type II achalasia on HRM. (*C*) Type III Achalasia on HRM. (*D*) EGJOO on HRM. [a] DL < 4.5 seconds. [b] Bolus pressurization. DL, distal latency; PEP, panesophageal pressurization. (*Courtesy of* the Esophageal Center of Northwestern, Chicago, IL; with permission.)

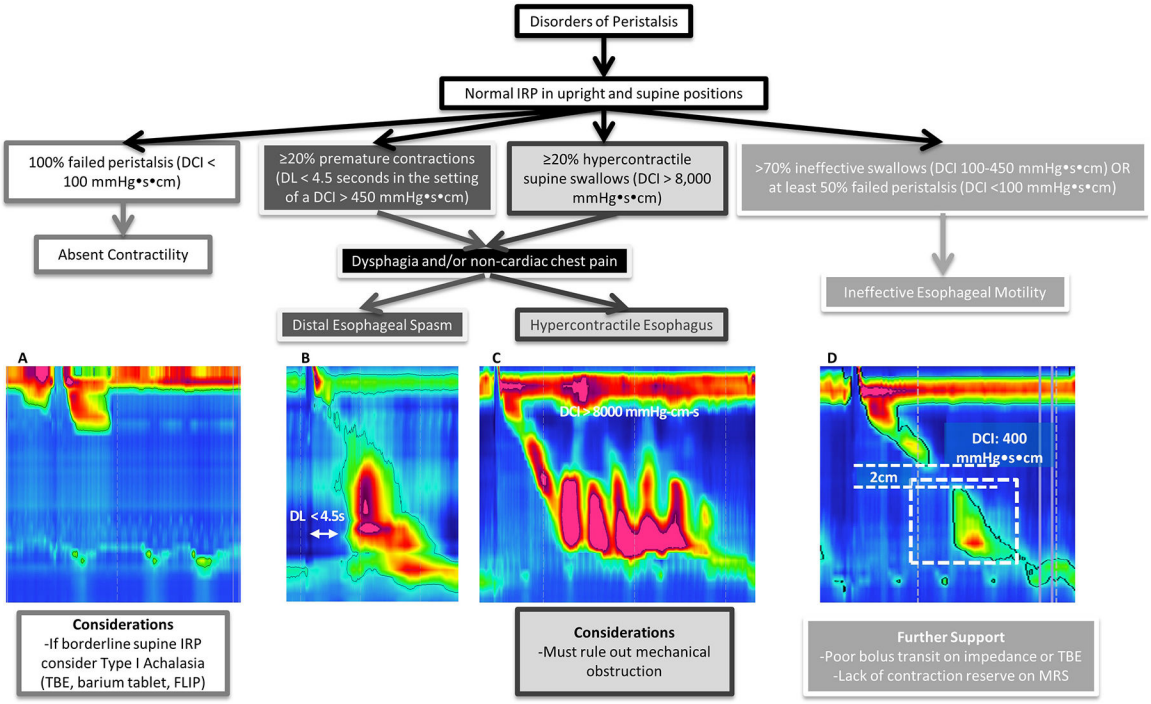

Fig. 2.

CCv4.0 disorders of peristalsis. The disorders of peristalsis. (*A*) Absent contractility on HRM. (*B*) DES on HRM. (*C*) Hypercontractile esophagus on HRM. (*D*) IEM on HRM. (*Courtesy of* the Esophageal Center of Northwestern, Chicago, IL; with permission.)

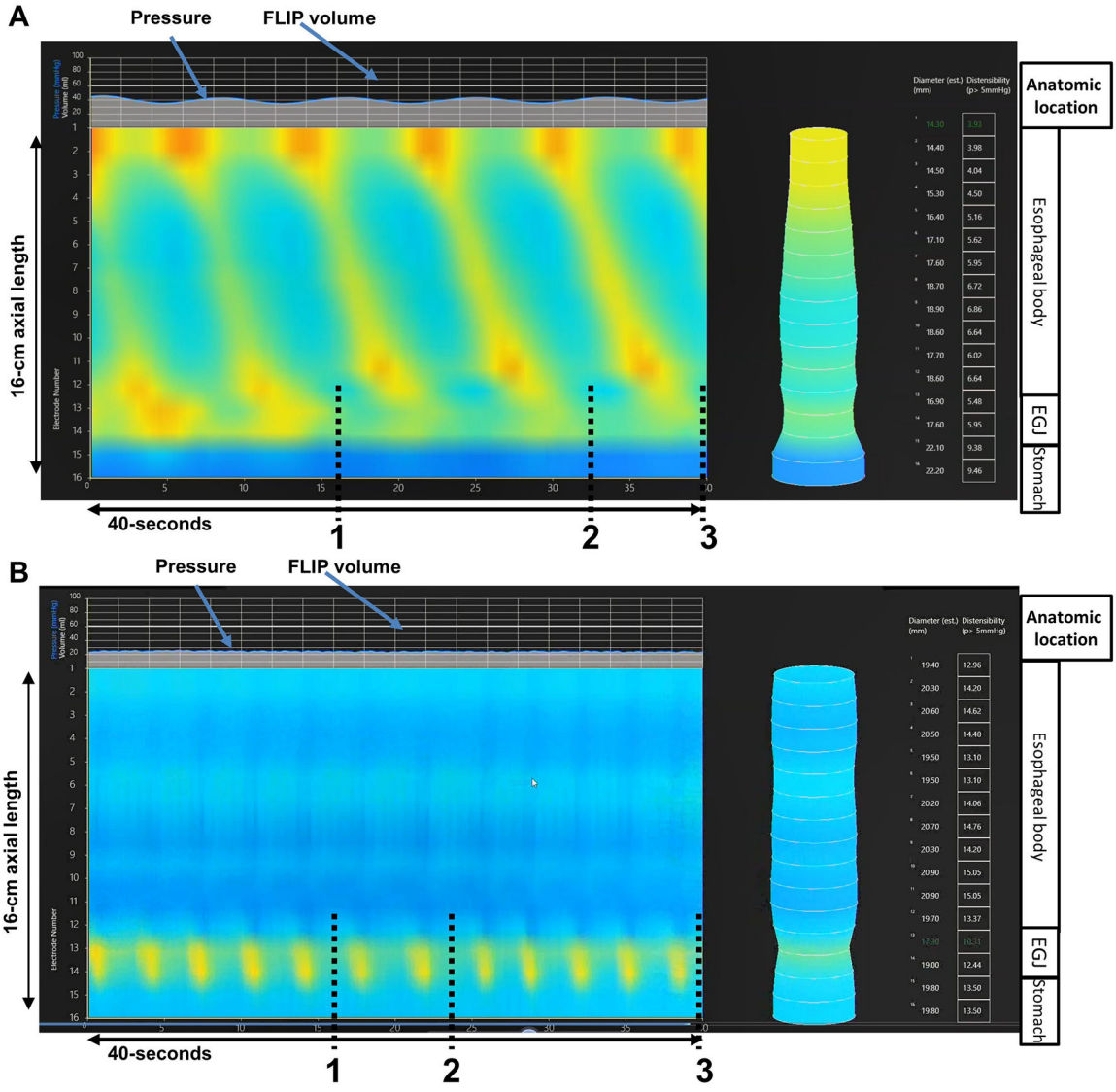

Fig. 3.

Evaluation of EGJ opening with FLIP panometry. Real-time FLIP panometry output from 2 patients (*A*, *B*) as 40 seconds of length (16 cm) × time × color-coded diameter FLIP topography (*bottom left*), with corresponding intraballoon pressure and FLIP fill volume (*top panels*). The hourglass-like image to the right reflects the FLIP at the instant corresponding to the far right of the topography plot; the narrowed region of the balloon ("waist") is at the EGJ. Evaluation of EGJ opening is related to presence (as in panel A) or absence (as in panel B) of antegrade contractions. EGJ opening is assessed at the peak diameter of EGJ opening, reflected by the vertical dashed lines in panels A and B. This occurs related to the pressure ramp or peak associated with contractions in panel A and is measured during expiration (ie, in-between crural contractions) in panel B. The median of 3 values of EGJ-DI is applied to reflect potential dynamic changes in EGJ opening. The patient in panel A had an HRM classified as normal motility; the patient in panel B

had systemic sclerosis and an HRM with absent contractility. (*Courtesy of* the Esophageal Center of Northwestern, Chicago, IL; with permission.)

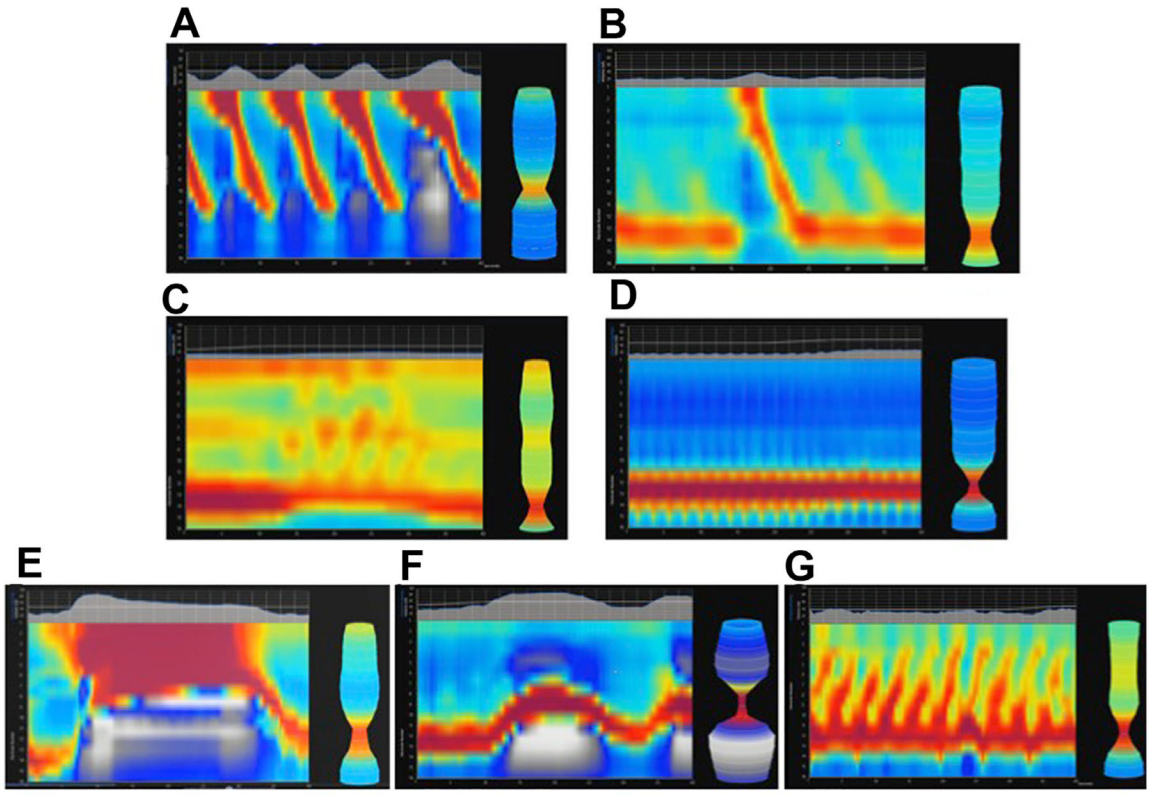

Fig. 4.

FLIP panometry contractile response patterns. Real-time FLIP panometry output from 7 different patients (*A*–*G*). (*A*) Normal contractile response defined by the RAC Rule-of-6s with ≥6 consecutive antegrade contractions of ≥6 cm in axial length occurring at a regular rate of 6 ± 3 antegrade contractions per minute. (*B*) Borderline contractile response defined as presence of a distinct antegrade contraction (≥6 cm in axial length), but not meeting the RAC Rule-of-6s. (*C*) Impaired-disordered contractile response defined as the presence of contractility, but without distinct antegrade contraction and not meeting criteria for a spastic-reactive response (*E*–*G*). (*D*) Absent contractile response defined by the absence of contractility. A spastic-reactive contractile response was defined by the presence of sustained occluding contraction (SOC) (*E*), a sustained lower-esophageal sphincter contraction (sLESC) (*F*), or repetitive retrograde contractions (RRCs) (*G*). (*E*) SOC, defined as a nonpropagating, occluding contraction of the esophageal body that persisted for greater than 10 seconds, occurred in continuity with the EGJ and was associated with a pressure increase greater than 35 mm Hg. (*F*) sLESC were defined as a transient reduction in diameter attributed to the LES that lasted greater than 5 seconds, was not associated with crural or antegrade contraction, and was associated with an increase in FLIP pressure. (*G*) RRCs were defined by greater than 6 consecutive retrograde contractions at a rate of greater than 9 contractions per minute. Also note the gray-dark blue areas observed concurrently with occluding contractions in panels A, E, and F reflect areas of the FLIP study that are impacted by dry catheter artifact: the esophageal diameters within these affected areas should be omitted from interpretation of the FLIP study. (*Courtesy of* the Esophageal Center of North-western, Chicago, IL; with permission.)

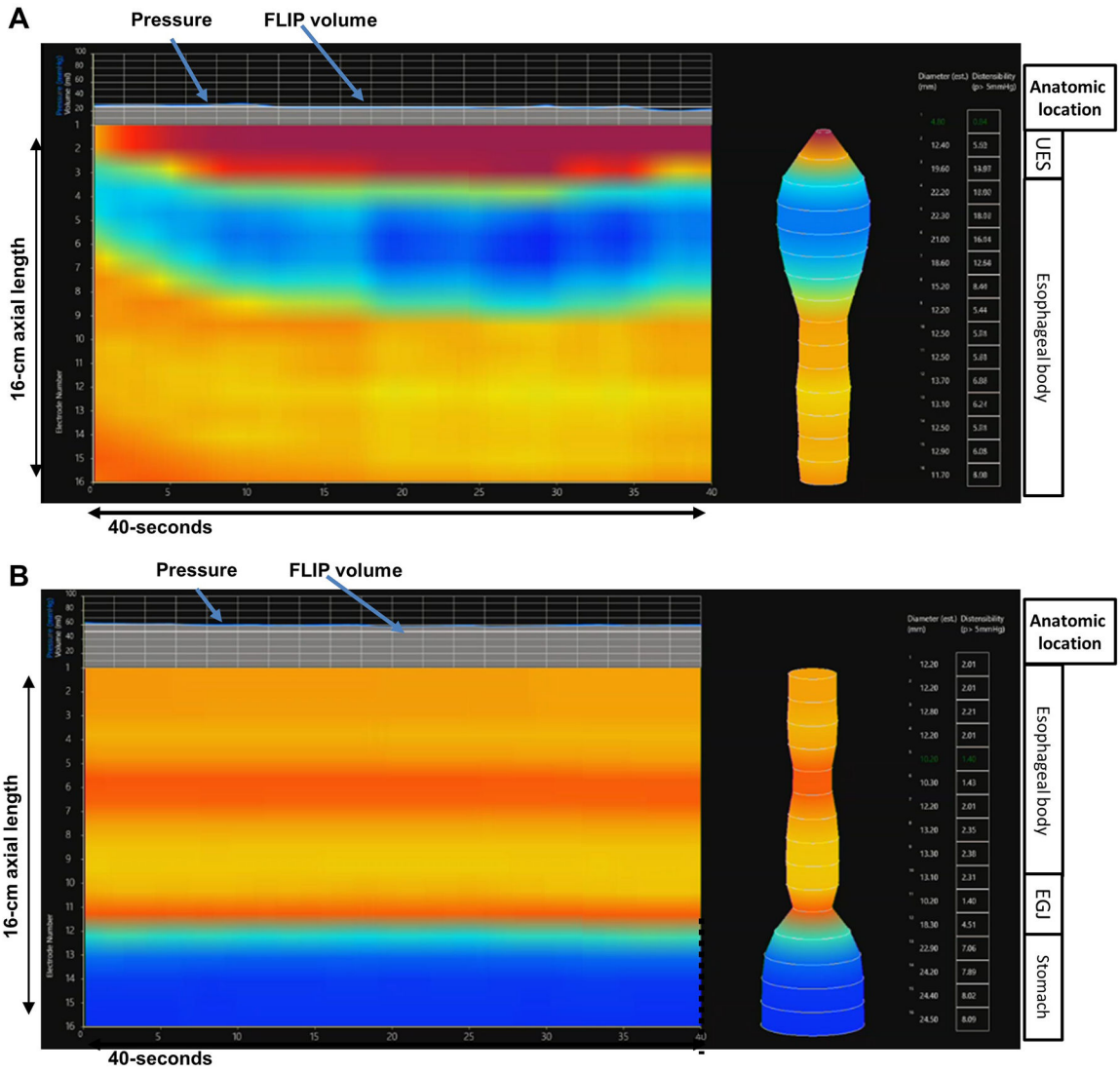

Fig. 5.

FLIP panometry in EoE. Real-time FLIP panometry output from a patient (*A*, proximal esophagus; and *B*, distal esophagus) with a narrow caliber esophagus from EoE. The distensibility plateau was 10.2 mm in the distal esophagus (*B*) and 12.2 mm in the proximal esophagus (*A*). UES, upper-esophageal sphincter. (*Courtesy of* the Esophageal Center of Northwestern, Chicago, IL; with permission.)

Table 1

High-resolution manometry test maneuvers

Test/Maneuver	Protocol	Diagnostic Utility	
Multiple rapid swallows (MRS)	In the upright position, five 2-mL wet swallows using a 10-mL syringe and occurring at 2- to 3-s intervals[3,79]	**1**	A normal response occurs when no esophageal body contractility is observed (DCI < 100 mm Hg•s•cm) and there is deglutitive inhibition during the repeat swallows, with post-MRS contraction augmentation (DCI post-MRS greater than each single swallow mean DCI)[3,39,79,80]
		2	Assessing the inhibitory and excitatory mechanisms within the esophagus and helping to determine peristaltic reserve, especially in association with gastroesophageal reflux[39,79,81]
		3	Lack of contractile reserve can be used to support a diagnosis of IEM[3,39]
		4	An elevated IRP >12 mm Hg during the MRS and RDC in patients with an elevated IRP in both the supine and upright positions supports a diagnosis of EGJOO[35]
Rapid drink challenge (RDC)	In the upright position, the patient drinks 200 mL of water as quickly as possible through a straw[3,82]	**1**	A normal response occurs when there is no esophageal body contractility (DCI < 100 mm Hg•s•cm) and complete deglutitive inhibition during this protocol[3,20,82,83]
		2	An elevated IRP >12 mm Hg plus panesophageal pressurization during the RDC may be more suggestive of EGJOO[3,20,35,82,83]
Solid test swallow and solid test meal (STM)	Solid test swallow involves 10 swallows of ~1 cm^3 of a soft solid and the STM involves consuming 200 g of a soft solid meal and must be completed in 8 min[3]	**1**	A normal response occurs when the patient is asymptomatic during the study; >20% of pharyngeal swallows are present, and it is followed by a normal esophageal contraction (DCI > 1000 mm Hg•s•cm) and without a significant break of >5 cm in the contractile front[3]
		2	Help determine if EGJ obstruction, postprandial rumination, or belching disorder is present[3]
		3	An elevated IRP with symptoms of dysphagia is suggestive of EGJOO[3]
Pharmacologic provocation (amyl nitrate & cholecystokinin [CCK])	4–5 sniffs of amyl nitrite in the recumbent position OR administration of 40 ng/kg of CCK intravenously in the recumbent position[3]	**1**	In achalasia and functional EGJOO, amyl nitrite causes a larger EGJ pressure drop (≥10 mm Hg) when compared with the deglutitive IRP[3]
		2	Can help distinguish which patients with EGJOO may have an early form of achalasia and thus may benefit from achalasia treatments[17]
		3	With CCK administration, achalasia patients experience an EGJ contraction of >50 mm Hg[3]
		4	Can help distinguish between opioid-induced type III achalasia and idiopathic type III achalasia[84]

Table 2

High-resolution manometry values. Medtronic, Inc, Shoreview, MN, USA. Laborie/Diversatek, Portsmouth, NH, USA

Value	Meaning	Interpretation[3]
Integrated relaxation pressure (IRP)	Assess the pressure during relaxation at the level of the esophagogastric junction	• Abnormal if supine … median IRP ≥ 15 mm Hg (Medtronic) • Abnormal if upright … median IRP ≥ 22 mm Hg (Laborie/Diverstatek) • Abnormal if upright … median IRP ≥ 12 mm Hg (Medtronic) • Abnormal if upright … median IRP ≥ 15 mm Hg (Laborie/Diversatek)
Distal contractile integral (DCI)	Measures the contractile vigor during esophageal peristalsis	• Normal: DCI 450–8000 mm Hg•s•cm • Failed: DCI < 100 mm Hg•s•cm • Hypercontractile: DCI > 8000 mm Hg•s•cm • Ineffective: weak contraction or failed peristalsis. Peristaltic break >5 cm in setting of DCI ≥ 450 mm Hg•s•cm
Distal latency (DL)	Deglutitive inhibition latency	• Premature/spastic: DL < 4.5 s in setting of DCI ≥ 450 mm Hg•s•cm
Isobaric contour	Pressurization	• Panesophageal pressurization: Isobaric contour of ≥30 mm Hg • Intrabolus pressurization: Isobaric contour of ≥20 mm Hg in supine position (Medtronic)

Table 3

Functional luminal imaging probe device characteristics and protocol

FLIP Length	**16 cm**	**8 cm**
Sensors	• 16 sensors • 1-cm spacing	• 16 sensors • 0.5-cm spacing
Assessment in esophageal syndromes	• EGJ • Esophageal body characteristics – Contractile response – Distensibility	• EGJ
Balloon length	16 cm	8 cm
Pressure reference	Atmospheric	Atmospheric
Placement	Transoral	Transoral
Baseline positioning	• Balloon should span the EGJ • 2–3 sensors distal to the EGJ	• Balloon should span the EGJ • EGJ waist at midballoon
Baseline fill volume	30 mL	20 mL
Baseline wait time	15 s	15 s
Pressure reference	Atmospheric	Atmospheric
Balloon fill protocol	40 mL, 50 mL, 60 mL, 70 mL	30 mL, 40 mL, 50 mL
Time at each fill level	60 s	30 s
Measurements	• EGJ-DI • EGJ-diameter • Intrabag pressure • Contractile response pattern • Esophageal body distensibility	• EGJ-DI • EGJ-diameter • Intrabag pressure