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Advances in the Diagnosis and Management of Achalasia and Achalasia-Like Syndromes: Insights From HRM and FLIP

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Abstract

High-resolution manometry, Chicago Classification v4.0, the functional lumen imaging probe, Panometry, and peroral endoscopic myotomy (POEM) are all now integral parts of the landscape for managing achalasia or, more precisely, achalasia-like syndromes. This narrative review examines the impact of these innovations on the management of achalasia-like syndromes. High-resolution manometry was the disruptive technology that prompted the paradigm shift to thinking of motility disorders as patterns of obstructive physiology involving the esophagogastric junction and/or the distal esophagus rather than as siloed entities. An early observation was that the cardinal feature of achalasia—impaired lower esophageal sphincter relaxation—can occur in several subtypes: without peristalsis, with pan-esophageal pressurization, with premature (spastic) distal esophageal contractions, or even with preserved peristalsis (esophagogastric junction outlet obstruction). Furthermore, there being no biomarker for achalasia, no manometric pattern is perfectly sensitive or specific for ‘achalasia’ and there is also no ‘gold standard’ for the diagnosis. Consequently, complimentary physiological testing with a timed barium esophagram or functional lumen imaging probe are employed both to improve the detection of patients likely to respond to treatments for ‘achalasia’ and to characterize other syndromes also likely to benefit from

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These authors report the following: John E. Pandolfino, Peter J. Kahrilas, and Northwestern University hold shared intellectual property rights and ownership surrounding FLIP Panometry systems, methods, and apparatus with Medtronic Inc. Peter J. Kahrilas: Ironwood (Consulting); Reckitt (Consulting), Phathom (consulting). Dustin A. Carlson: Medtronic (Speaking, Consulting); Phathom Pharmaceuticals (Consulting). John E. Pandolfino: Sandhill Scientific/Diversatek (Consulting, Speaking, Grant), Takeda (Speaking), Astra Zeneca (Speaking), Medtronic (Speaking, Consulting, Patent, License), Torax (Speaking, Consulting), Ironwood (Consulting).

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achalasia therapies. These findings have become particularly relevant with the development of a minimally invasive technique for performing a tailored esophageal myotomy, POEM. Now and in the future, optimal achalasia management is to render treatment in a phenotype-specific manner, that is, POEM calibrated in a patient-specific manner for obstructive physiology including the distal esophagus and more conservative strategies such as a short POEM or pneumatic dilation for obstructive physiology limited to the lower esophageal sphincter.

Keywords

Dysphagia; Achalasia; Functional lumen imaging probe; Manometry; Esophagus

Introduction

The universe of esophageal motility disorders has seen a series of major changes in conceptualization, diagnostic instruments, diagnostic algorithms, and therapeutics over the last 2 decades. High-resolution manometry (HRM) is now firmly entrenched in motility laboratories around the world and the Chicago Classification, now in v4.0, is uniformly accepted as the consensus statement on HRM interpretation.[1] Per Oral Endoscopic Myotomy (POEM) has largely replaced laparoscopic Heller myotomy (LHM) and pneumatic dilation (PD) as first-line therapy for achalasia, especially spastic achalasia, in esophageal tertiary care centers.[2–4] Intraoperative functional lumen imaging probe (FLIP) measurements are being used to calibrate the myotomy for achalasia.[5,6] FLIP panometry is being adopted as a diagnostic tool used in conjunction with endoscopy to diagnose achalasia and achalasia-like syndromes both on its own and to clarify equivocal HRM findings.[1,7–9] All of this is relatively new. A mere 15 years ago, ‘experts’ were still debating the merits of HRM verses three-channel line-tracing manometry, a technology now as obsolete as a typewriter.

Achalasia-like syndromes

A fundamental innovation of HRM was changing the presentation format of motility data from line tracings to pressure topography or Clouse plots.[10] Pressure topography plots use a coordinate system of time on the x-axis, sensor position on the y-axis, and pressure values as spectral color within that grid. This elegantly condenses an enormous dataset of 36 pressure sensors sampling at a rate of 40 Hz into a single image that makes sphincters, propagated or nonpropagated contractions, luminal pressure gradients, and isobaric regions within the esophagus visually obvious. Hence, in a way never achieved with line-tracing manometry, HRM revealed patterns of obstructive physiology, both at the esophagogastric junction (EGJ) and along the esophageal lumen. An early outcome of this revolutionized visualization was the subtyping of achalasia based on the 3 major patterns of esophageal pressurization associated with outflow obstruction at the EGJ[11] (Figure 1). However, it has since become clear that obstructive physiology also occurs in syndromes besides achalasia involving the EGJ and/or distal esophagus. In fact, obstructive physiology is increasingly recognized as the fundamental abnormality leading to the perception of dysphagia with esophageal motility disorders.[12] This concept of obstructive physiology as the fundamental

abnormality has substantially morphed the clinical management of esophageal motility disorders.

Classification schemes are important in clinical management and the Chicago Classification has gone a long way in objectifying the diagnosis of achalasia. However, the fact that it has now gone through 4 iterations since 2008 emphasizes that this is a work in progress and that no classification scheme of esophageal motility disorders based on a single test will ever be perfect. After all, there are no biomarkers of esophageal motility disorders and, in the absence of a biomarker, there can be no 'gold standard' for diagnosis. Motility disorders are diagnosed based on abnormalities of esophageal function, not on the etiology of that dysfunction. Although we recognize that in pathology specimens sourced from advanced cases of achalasia, the underlying pathology is of a myenteric plexopathy,[13,14] the diagnosis is rarely, if ever, established by neuropathology. Instead, the diagnosis is established using physiological tests to demonstrate that symptomatic esophageal dysfunction (potentially dysphagia, regurgitation, or chest pain) is occurring as a result of esophageal obstruction that cannot be attributed to a stricture, tumor, prior surgery, vascular structure, implanted device, infection, or inflammatory process. Rather, the obstruction is caused by abnormal contractility, the impairment of normal neuronally mediated inhibition, or both. For achalasia-like syndromes, the contractile obstruction can be located at the lower esophageal sphincter (LES) or the LES along with the adjacent distal esophagus. The objective of physiological testing is to identify and localize the physiological obstruction so as to optimize treatment. Furthermore, it is noteworthy that most, but not all, muscularis propria biopsy specimens of these patients obtained in the course of a therapeutic myotomy exhibit the myenteric plexopathy described in advanced achalasia cases.[15,16] In one of those series, 3 of the 46 cases treated with a surgical myotomy exhibited apparently normal histopathology and one case had predominantly eosinophilic inflammation.[15] Similarly, it is now widely recognized that chronic opioid use can cause dysphagia and abnormal HRM patterns often mimicking type III achalasia.[17] Hence, the terminology 'achalasia-like syndromes'.

Given the diagnostic limitations discussed above, it is important to recognize the limitations of HRM with respect to the diagnosis and management of achalasia: (1) some patients with achalasia have an integrated relaxation pressure (IRP) < 15 mmHg, the widely accepted upper limit of normal; (2) there can be instances in which some peristalsis is preserved making the criterion of 'absent peristalsis' somewhat subjective; (3) the IRP performs poorly as an assessment of treatment outcome; (4) HRM is inherently better at quantifying contraction than detecting inhibition, which is an equally important determinant of normal esophageal motility; and (5) the distinction among achalasia subtypes can be blurred when underlying spastic contractility is obscured by panesophageal pressurization. Basically, the threshold for diagnosis and the distinction among achalasia subtypes (or between achalasia and nonachalasia) can be difficult and some cases have features of more than one subtype. Furthermore, as the disease develops over an unknown period of time, there is a transition from normal peristalsis and normal EGJ relaxation to absent peristalsis and impaired EGJ relaxation; at intermediate time points in the development of the disease, these abnormalities might or might not achieve the requisite diagnostic thresholds. Textbook cases will always be easy to diagnose, but no matter what your level of expertise, there will always

be ‘borderline’ cases in which clinical judgment rather than adherence to dichotomous numerical thresholds ends up being the final arbiter.

FLIP in the diagnosis of achalasia-like syndromes

One approach to clarifying inconclusive or equivocal HRM findings is to add provocative maneuvers such as multiple rapid swallows (5 sequential 2-mL swallows less than 4 seconds apart) or a rapid drink challenge (200 mL swallowed within 30 seconds) to the HRM protocol as advocated in Chicago Classification v4.0.[1,18] This is in recognizing that the cardinal abnormality in achalasia is obstructive physiology at the EGJ and that there can be relevant EGJ obstruction with a normal or even low IRP on HRM in the setting of absent contractility. An alternative (or additional) approach to an equivocal HRM diagnosis is to compliment the HRM study with a FLIP study. The FLIP measures EGJ distensibility, defined as EGJ opening diameter as a function of distending pressure. The FLIP device uses impedance planimetry to measure luminal cross-sectional area within a 15-cm span of the esophagus. The probe has a cylindrical, highly compliant bag at its distal end enclosing multiple impedance planimetry electrodes and a single pressure sensor. During a FLIP study, usually done in conjunction with endoscopy and using the same sedation as for the endoscopy, the probe is positioned across the EGJ, protruding slightly into the stomach. In some cases, endoscopic manipulation is needed to obtain proper positioning. The probe is then progressively filled with 50, 60, and 70 mL of saline to distend the distal esophagus and EGJ. The resultant distention-induced esophageal contractility is displayed topographically, analogous to pressure topography displays of HRM.[19] The difference between FLIP and HRM is that FLIP topography (Panometry) is a dynamic topographic plot of esophageal diameter along the length of the probe as opposed to HRM which is a dynamic topographical plot of resting and contractile pressure along the sensing catheter. Pressure is also recorded from within the FLIP probe but only from a single sensor which then allows for calculations of distensibility (mm^2/mmHg), a critical metric for assessing outflow obstruction. Hence, assessing esophageal motility with FLIP is based on characterizing distention-induced contractility in the distal esophagus and EGJ distensibility.

The bag encasing the FLIP sensors is flaccid to a fill diameter of ≈2 cm and then essentially noncompliant. It is made of a noncompliant plastic material, much like plastic wrap. Consequently, fluid moves easily within the FLIP probe and peristalsis progresses along the probe such that the topography display characterizes both its rate of progression and the extent of associated luminal occlusion in a real-time plot. With progression of a normal secondary peristaltic contraction, the distal end of the probe (situated in the stomach) fills to capacity and eventually pressurizes to a value more than that of the advancing contraction, at which point the fluid escapes retrograde back into the proximal segment of the probe, again distending the esophagus, and thereby stimulating another secondary peristaltic contraction. Hence, the normal pattern of contractility during FLIP Panometry is of repetitive antegrade contractions (RACs), defined as 6 repetitive contractions spanning at least 6 cm of the FLIP probe and occurring at a frequency of 6 ± 3 per minute. Among 35 normal volunteer subjects tested, 89% exhibited RACs while the other 11% also exhibited antegrade contractions but not sufficiently repetitive to meet the ‘rule of 6’, which was devised as an objective definition of RACs.[20,21] Notably, esophageal contractions can be

detected with Panometry even when they are not lumen occluding making them undetectable by HRM and explaining the 'recovery' of peristalsis often observe in HRM studies after achalasia treatments.[22,23] In actuality, the weak peristaltic contractions were always there but they were masked by the greater values of panesophageal pressurization attributable to EGJ outflow obstruction.

The FLIP correlate of impaired EGJ relaxation on HRM (IRP > 15 mmHg) is impaired EGJ opening as assessed with the distensibility index (DI) at the 60-mL fill volume and the maximal EGJ opening diameter achieved at the 60-mL or 70-mL fill volumes. The conceptual advantage of FLIP over HRM lies in the distinction between sphincter relaxation and sphincter opening. HRM measures relaxation; the FLIP quantifies opening. Although these are usually related, it is sphincter opening that determines the volume of bolus flow through the EGJ. Normal EGJ opening is defined as EGJ-DI ≥ 2.0 mm^2/mmHg and maximum EGJ diameter ≥ 16 mm. Reduced EGJ opening is defined as EGJ-DI < 2.0 mm^2/mmHg and maximum EGJ diameter < 12 mm. Patients not meeting either of these definitions are categorized as borderline opening.[24]

Following from the above, both HRM and FLIP Panometry have criteria for defining obstructive physiology at the EGJ, a prerequisite for diagnosing achalasia or achalasia-like syndromes. With HRM, a diagnosis of achalasia requires a high IRP and absent primary peristalsis, albeit often with other patterns of esophageal pressurization. Chicago Classification v4.0 differs from earlier versions in that it broadens the definition of a high IRP to include evidence of obstructive physiology gained from wet swallows in a secondary testing position (sitting vs supine or vice versa), during multiple repetitive swallows, or during a rapid drink challenge.[1,18] With FLIP, diagnosing an achalasia-like syndrome requires reduced EGJ opening and something other than a normal contractile response (RACs). The RAC pattern is uniformly lost in achalasia, seen in 0 of 224 patients with treatment naïve achalasia as defined by HRM (55 type I, 129 type II, 40 type III).[9] Instead, the achalasics had either a weak contractile response, absent contractile response, or a spastic-reactive contractile response (Figure 2). Furthermore, when antegrade or retrograde repetitive contractions are observed in achalasia, they occur at a faster frequency that the 6 ± 3 per minute of the normal RAC pattern. The differing frequency of repetitive contractions and the occurrence of retrograde repetitive contractions remains to be explained but is potentially related to diminished inhibitory myenteric plexus function, loss of connectivity to a central pattern generator linked to respiration, or even the intrinsic refractoriness of the esophagus after a contraction.[21] One could speculate that the pathophysiological difference between achalasia subtypes is the complete loss of myenteric neuron function in nonspastic achalasia as opposed to a selective loss of inhibitory myenteric neuron function in spastic achalasia. Agangionosis leads to a flaccid, dilated esophagus with persistent LES contraction attributable to residual myogenic tone. On the other hand, the selective loss of inhibitory myenteric neuronal function results in rapidly propagated contractions (even retrograde contractions on Panometry) along with greater LES pressure because of unopposed excitatory neuron stimulation. Whatever the explanation, FLIP distinguishes 2 subtypes of achalasia: spastic achalasia (with spastic-reactive contractile response) and nonspastic achalasia (with weak contractile response or absent contractile response). Do HRM and FLIP identify the same patients as having achalasia? Pretty much; in a study of

687 symptomatic patients evaluated with both tests and interpreted in a blinded fashion, HRM conclusively diagnosed achalasia in 224 and 223 (99.5%) of these had reduced EGJ opening on FLIP Panometry.[20] Evident by this concordance, there is a shared physiology between impaired LES relaxation on HRM and reduced EGJ opening on FLIP.

Esophagogastric junction outflow obstruction

HRM unquestionably advanced our understanding of esophageal motility disorders and certainly improved our ability to diagnose achalasia as evidenced by a study suggesting that the adoption of HRM in a motility laboratory led to a 3-fold increase, the estimate of the disease incidence in the surrounding area.[25] Furthermore, HRM seemed to detect cases of an achalasia-like syndrome characterized by obstructive physiology at the EGJ (usually defined as an IRP > 15 mmHg) along with sufficiently preserved peristalsis to exclude a diagnosis of achalasia.[26] In the Chicago Classification, this entity was labeled EGJ outflow obstruction (EGJOO), a heterogenous group including cases of ‘variant’ achalasia, obstructive hiatus hernia, manometric artifact, opiate effect, abdominal obesity, and normal individuals. Laboratories around the world reported the prevalence of EGJOO to range between 5% and 24% of all HRM studies in a multitude of published cohorts.[27] Given that only a fraction of these individuals actually had clinically relevant obstructive physiology at the EGJ, caution has always been advised in the management of EGJOO patients, avoiding achalasia treatments in most of them because published series concluded that anywhere from 32% to 94% of EGJOO patients did not require any therapy.[27] However, in the era of Chicago Classification v3.0, this cautionary advice was often ignored leading to the inappropriate treatment of many EGJOO patients as ‘variant’ achalasia. In fact, such overdiagnosis and overtreatment was a major impetus for formulating Chicago Classification v4.0.

Apart from using provocative maneuvers during the HRM study, Chicago Classification v4.0 advocates using ancillary testing with FLIP or timed barium esophagram to clarify the significance of EGJOO on HRM. With a timed barium esophagram, the patient drinks 200 mL of low-density barium in an upright posture followed by frontal x-rays 1, 2, and 5 minutes afterward. The degree of esophageal emptying is then estimated by measuring the height of the residual barium column in the esophagus. The most robust outcome measure is the height of the barium column at 5 minutes with the proposed critical threshold ranging from 2–5 cm.[26,28] When a 12-mm barium tablet is used in conjunction with the timed barium esophagram, a secondary criterion of abnormality is for the tablet to become lodged at the EGJ. A positive timed barium esophagram is strong supportive evidence of functionally significant EGJ outflow obstruction and a completely normal study makes an achalasia diagnosis highly unlikely.[29] Analogous data can be obtained using HRM with impedance in an upright posture and using the impedance electrodes to ascertain the height of retained fluid in the esophagus at a 5-minute interval.[30] However, these tests are not as definitive in evaluating EGJOO as they are for achalasia because bolus clearance may not be compromised in EGJOO. FLIP, on the other hand, yields an assessment of EGJ obstructive physiology that is independent of the esophageal contractile response making it more useful in this circumstance.

The Chicago Classification v4.0 working group tasked with evaluating the EGJOO conundrum formulated a technical note on the topic along with a series of recommendations to guide management.[27] Recommendations required agreement by ≥ 80% of the working group and were assigned a strength of recommendation along with an evaluation of the quality of supportive evidence. The most noteworthy conclusion from the working group was that an isolated manometric diagnosis of EGJOO should always be considered clinically inconclusive. To become actionable that findings must be supported by the presence of clinically relevant symptoms (chest pain or dysphagia) and at least one of the other testing modalities (timed barium esophagram, preferably with a tablet, or FLIP) that confirmed EGJ obstructive physiology. Basically, there is no 'gold standard' for a conclusive (actionable) EGJOO diagnosis and it takes at least 2 positive complementary studies to establish the diagnosis. In instances when all 3 studies (HRM, FLIP, and timed barium esophagram) are available and there is discordance, the majority rules, potentially negating the findings from any one of them.

The recommendations of the Chicago Classification v4.0 working group on EGJOO were subsequently tested in an observational study of a 139 EGJOO patient cohort who were all evaluated with both HRM and FLIP.[8] A substantial fraction of the cohort also had data available from timed barium esophagram and/or a rapid drink challenge as part of their HRM study. The corresponding FLIP Panometry EGJ opening classifications in this EGJOO 'inconclusive' cohort were reduced EGJ opening in 48%, borderline EGJ opening in 30%, and normal EGJ opening in 22%. The FLIP contractile response patterns were normal in 6%, borderline in 21%, impaired/disordered CR in 43%, absent contractile response in 17%, and spastic-reactive in 14%. Applying both the EGJ and contractile response classifications, the final FLIP Panometry classifications were 'normal' in 21%, thereby refuting the HRM classification of EGJOO. On the other hand, the FLIP Panometry was supportive of either EGJ obstruction with weak contractile response or spastic-reactive contractile response supporting a clinically relevant diagnosis of conclusive EGJOO in 49% of the cohort but still leaving 29% as 'inconclusive'. Notably, 77% of the conclusive EGJOO patients reported significant clinical improvement following achalasia-type treatments as judged by an improved Eckhardt score. This compared to no significant improvement in 12 of 12 patients; such patients managed with a 'non-achalasia' treatment approach. Figure 3 details the comprehensive evaluation of this patient cohort emphasizing the complimentary nature of these function tests and that, even using the updated criteria in Chicago Classification v4.0, EGJOO remains an entity associated with clinical heterogeneity and, ultimately, still some instances of diagnostic uncertainty.

Personalized, phenotype-directed treatment

With the widespread adoption of POEM, it now joins PD and LHM as a highly efficacious and durable treatment approach for achalasia. However, it has also complicated the discussion of which therapy is optimal for which patient. There are published randomized control trials (RCTs) comparing LHM to POEM,[3] LHM to PD,[31–34] and POEM to PD[2,35] but no 3-armed RCT. In these trials, the efficacy of LHM or POEM was uniformly in the 90% range while that of PD ranged from 54%[35] to 86%.[31] The variable response to PD speaks to the nonstandardized protocols by which it is done, variable employing dilators

to a maximum or 35-mm or 40-mm diameter and variably allowing for repeated dilations with recurrence of dysphagia as part of the PD protocol or not. This variability in PD protocol necessarily weakens the findings of a network meta-analysis seeking to integrate the entire dataset of RCTs because the PD arms are not comparable from one trial to another. Nonetheless, a recent attempt at doing just that concluded that POEM and LHM have equal efficacy and both are more effective than PD.[36] Other limitations of the RCT data are that advanced achalasia cases were variably included or excluded from the study populations and, most significantly, that there was no prospective subtyping of achalasia.

All subtypes of achalasia share the common element of impaired EGJ relaxation and reduced EGJ opening, but the associated pattern of esophageal contractility varies from absent contractility at one extreme to spastic contractions involving the entire smooth muscle esophagus at the other. An immediate observation with the description of achalasia subtypes in 2008 was that treatment outcome varied with subtype such that the best treatment outcomes were seen in type II and the worst in type III.[11] Those observations were subsequently confirmed by a number of other studies[37–40] and by a systematic review and meta-analysis exploring a multitude of potentially factors relevant to treatment outcome.[41] After assessing 117 relevant citations for potential patient-specific predictors of treatment outcome, the meta-analysis concluded that most putative predictors were inconsistent among studies and only age (younger patients did worse), manometric subtype (type III did worse), and the presence of sigmoid-shaped esophagus (did worse) were classified as predictors with a strong level of cumulative evidence. Poor outcomes with sigmoid esophagus are understandable as these patients often have chronic esophageal retention with a sink-trap deformity at the distal end. In that circumstance, simply eliminating the outflow obstruction might not suffice to facilitate esophageal emptying, especially when the chronic esophageal retention is combined with the complete absence of distal esophageal contractility. Alternatively, poor treatment outcomes with type III achalasia are attributable to persistent obstructive physiology in the distal esophagus that may be inadequately addressed with LES-targeted treatment. Also, of course, none of these trials included patients with achalasia-type EGJOO. Taken together, all of these considerations enhance the appeal of phenotype-directed treatment.

To date, there are no RCT data on achalasia management that prospectively consider achalasia subtype in their design or in their assessment of treatment efficacy. However, retrospective analysis of RCT data exemplified by the European achalasia trial[31] suggests that achalasia subtypes are of great relevance in forecasting treatment effectiveness. Indeed, in the European achalasia trial, the efficacy of PD for treating type II achalasia was 100%, significantly better LHM (93%, $P = .03$), whereas treatment success in type 3 achalasia was 40% and 86% for PD and LHM, respectively (although this difference was not statistically significant because of small numbers of patients, n = 10 and 8, respectively).[39] Subsequently, an excellent meta-analysis was published identifying all relevant articles reporting clinical outcomes of patients with achalasia classified by manometric subtype after botulinum toxin injection, PD, LHM, and POEM.[4] Data from that meta-analysis summarized in Figure 4 concluded that (1) POEM was more successful than LHM for both type I (oods ratio [OR] 2.97, $P = .03$) and type III achalasia (OR 3.50, $P = .007$), (2) POEM was the most efficacious treatment across the entire achalasia spectrum with pooled response

rates of 95%, 97%, and 93% for type I, II, and III achalasia, respectively, (3) PD had a lower but not significantly different success rate compared with POEM or LHM in type II achalasia, and (4) botulinum toxin injection was inferior in all subtypes.

The widespread adoption of POEM in esophageal tertiary care centers around the world has clearly been a major development in achalasia therapeutics.[42] The POEM procedure involves making a submucosal tunnel from the midesophagus to the gastric cardia and then performed a circular muscle myotomy from within the submucosal tunnel, beginning at the gastric cardia and progressing proximally across the LES.[43] Therein lies the key advantage of POEM over LHM; the myotomy performed with POEM can be longer if desired, potentially extending along the entire length of smooth muscle esophagus, whereas in LHM it is limited to the length of esophagus that can be safely accessed from below the diaphragm. This benefit is most apparent in treating patients with distal esophageal obstructive physiology such as type III achalasia. Supportive of that hypothesis, in a meta-analysis of uncontrolled POEM series, Khan *et al.* reported a weighted pooled response rate of 92% (95% CI 84%–96%) in type III achalasia with a mean length of myotomy of 17.2 cm (range 13.0–19.7 cm).[44] Furthermore, treatments effective for type III achalasia should also be effective for other disorders characterized by obstructive physiology of the distal esophagus, notably distal esophageal spasm and hypercontractile esophagus. The meta-analysis by Khan *et al.* reported a weighted pooled response rate of 72% (95% confidence interval [CI] 55%–83%) in ‘jackhammer’ esophagus and of 88% (95% CI 61%–97%) in distal esophageal spasm, only 4% less than in type III achalasia. However, it must be emphasized that these data are from short-term uncontrolled studies without standardization of how the appropriate myotomy length was determined.

Although we have come a long way in the diagnosis and treatment of achalasia, no current treatment is curative and the overall treatment efficacy declines over time regardless of which treatment is rendered. Long-term treatment failure rates following LHM or PD have been reported to range from 18%–35%.[40,45] The likelihood and mechanism of treatment failure varies with the specific treatment and achalasia subtype but can be attributable to post-treatment reflux, recurrent dysphagia, the development of esophageal hypersensitivity, formation of a pseudodiverticula at the myotomy site (also known as a blown out myotomy or BOM),[46] or progression of esophageal dilatation. In extreme cases of treatment failure, often after multiple LES-targeted interventions, esophagectomy may be required in patients with end-stage achalasia to restore alimentary transit, reverse nutritional deficiencies, prevent recurrent aspiration pneumonia, or because of the development of squamous cell cancer, the incidence of which has been estimated to be about 3 per 1000 patient-years follow-up.[47] A systematic review and meta-analysis of esophagectomy for end-stage achalasia identified 8 published series inclusive of 1307 patients.[48] The most common indication for esophagectomy was of severe symptoms with radiographic findings of a sigmoid esophagus. The stomach was used as a conduit in 95% of these cases with a colonic interposition being the main alternative. Postoperative morbidity ranged from 19% to 50% with pneumonia and anastomotic leaks being the most reported complications. Mortality ranged from 0% to 5.4% among series.

Post-treatment reflux

It stands to reason that surgical myotomy of the LES can result in problematic acid reflux. With LHM, this risk is mitigated by pairing the myotomy with a partial fundoplication, be that a posterior 270° Toupet fundoplication or an anterior 180° Dor fundoplasty. Initially, it was hoped that GERD would be infrequent following a POEM procedure given the absence of hiatal dissection or gastric mobilization. However, subsequent studies have suggested that GERD is more common following POEM compared with PD and LHM. Indicative of this, a multicenter RCT of 221 patients with achalasia found that erosive esophagitis was more common following POEM from LHM at 3 months (57% vs 20%) and 24 months (44% vs 29%).[3] Similarly, a meta-analysis comparing 1542 POEM and 2581 LHM patients reported that symptomatic GERD (19% vs 8.8%), abnormal pH-metry (39% vs 16.8%), and erosive esophagitis (29.4% vs 7.6%) were all more common after POEM than LHM.[49] However, the clinical significance of this has been questioned given that despite 47% of 2373 post-POEM patients having abnormal pH-metry, only 8.5% were symptomatic.[50] Similarly, most post-POEM esophagitis is mild (Los Angeles A or B) and in the RCT comparing LHM to POEM, there was no significant difference in the occurrence of Los Angeles C or D esophagitis.[3] Nonetheless, modifications to the intraoperative POEM technique such as shortening the myotomy, avoiding dividing the gastric sling fibers by orienting the myotomy along the lesser curve, and using intraoperative FLIP to calibrate the myotomy have all been suggested as a way of minimizing post-POEM reflux.[51]

Conclusion

HRM and analysis algorithms recently updated in the Chicago Classification v4.0 have led to a paradigm shift to thinking of motility disorders as patterns of obstructive physiology involving the EGJ and/or the distal esophagus rather than as siloed entities. The cardinal feature of achalasia, impaired LES relaxation, is now recognized to occur in several disease phenotypes: with absent contractility, with premature (spastic) distal esophageal contractions, with pan-esophageal pressurization, or with some preserved peristalsis. An immediate effect of this advance has been increased detection of achalasia, challenging previous epidemiological estimates of the incidence and prevalence of this disorder. Furthermore, without a disease-specific biomarker, no manometric pattern is absolutely sensitive or specific for idiopathic achalasia caused by a myenteric plexopathy and physiological testing reveals other syndromes involving physiological obstruction but not meeting Chicago Classification criteria for achalasia, which also benefit from therapies formerly reserved for achalasia. Complimentary assessment with timed barium esophagram, FLIP, or provocative maneuvers done in conjunction with HRM can be useful in defining these syndromes. The utility of these additional clinical assessment techniques has become particularly relevant with the development of the POEM procedure, an endoscopic technique for performing a calibrated myotomy of the esophageal circular muscle that can be done on outpatients. Hence, with HRM and the Chicago Classification v4.0, we have come to conceptualize esophageal motility disorders by specific aspects of physiological dysfunction, potentially involving the LES and/or obstructive physiology of the distal smooth muscle esophagus. A major implication of this approach is a shift in management strategy toward rendering treatment in a phenotype-specific manner, for example, POEM

calibrated to patient-specific physiology as defined by HRM for the spastic disorders and more conservative strategies such as a short POEM or PD for obstructive physiology limited to the LES.

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Abbreviations used in this paper:

BOM	blown out myotomy
CI	confidence interval
DI	distensibility index
EGJ	esophagogastric junction
EGJOO	EGJ outflow obstruction
FLIP	functional lumen imaging probe
HRM	High-resolution manometry
IRP	integrated relaxation pressure
LES	lower esophageal sphincter
LHM	laparoscopic Heller myotomy
OR	odds ratio
PD	pneumatic dilation
POEM	per-oral endoscopic myotomy
RAC	repetitive antegrade contraction
RCT	randomized control trial

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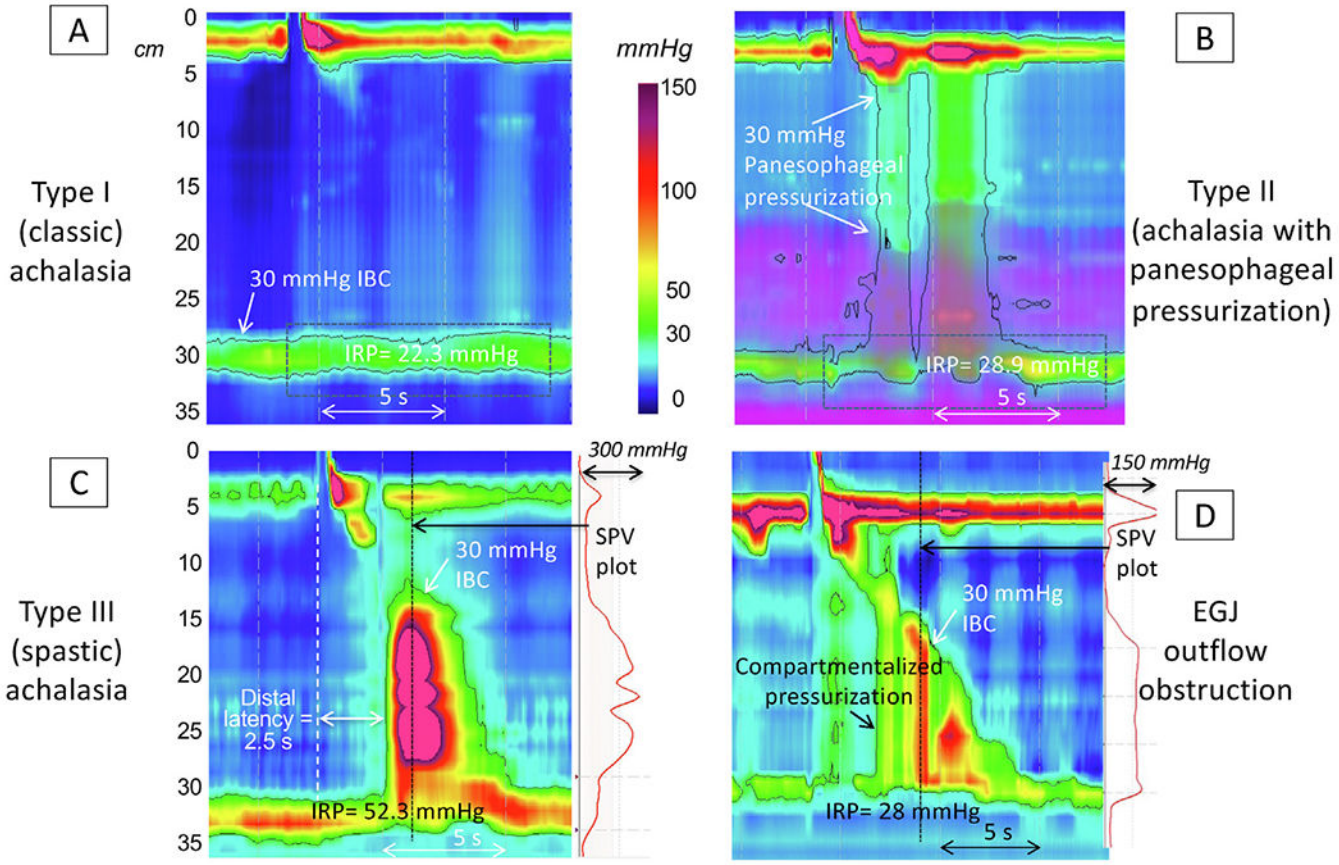

Figure 1.

Achalasia subtypes and achalasia-type esophagogastric (EGJ) outflow obstruction. A. Type I achalasia: integrated relaxation pressure (IRP) is elevated (> 15 mmHg) with 100% failed peristalsis (distal contractile index [DCI] < 100 mmHg•s•cm), and without panesophageal pressurization. B. Type II achalasia: IRP is elevated with 100% failed peristalsis and panesophageal pressurization to > 30 mmHg observed in ≥ 20% of test swallows. Note that this recording was obtained with an impedance-manometry catheter with the impedance signal (evident by the purple shading) showing retained fluid in the distal half of the esophagus. On timed barium esophagram, the level of barium retention would correspond to the level of purple shading. C. Type III achalasia: IRP is elevated with a normal DCI (> 450 mmHg•s•cm), and premature contractions (distal latency < 4.5s). D. EGJ outflow obstruction: IRP is elevated with preserved peristalsis and compartmentalized pressurization between the peristaltic contraction and the EGJ. Note the differences between the spatial pressure variation (SPV) plots to the right of the type III achalasia and EGJ outflow obstruction panels. The SPV plots illustrate the top-to-bottom pressure profile within the Clouse plot at the time indicated by the black dashed line. In type III achalasia this has multiple peaks indicating multiple points of luminal closure, often reported as a ‘corkscrew’ or ‘rosary bead’ on an esophagram and interpreted as distal esophageal spasm, while with compartmentalized pressurization, the zone of pressurization is a flat plateau, indicating pressurization within a chamber sealed at both ends. This would also be the case with type II achalasia except the plateau extends from the upper sphincter to the lower sphincter making

it panesophageal pressurization. Figure used with permission from the Esophageal Center at Northwestern.

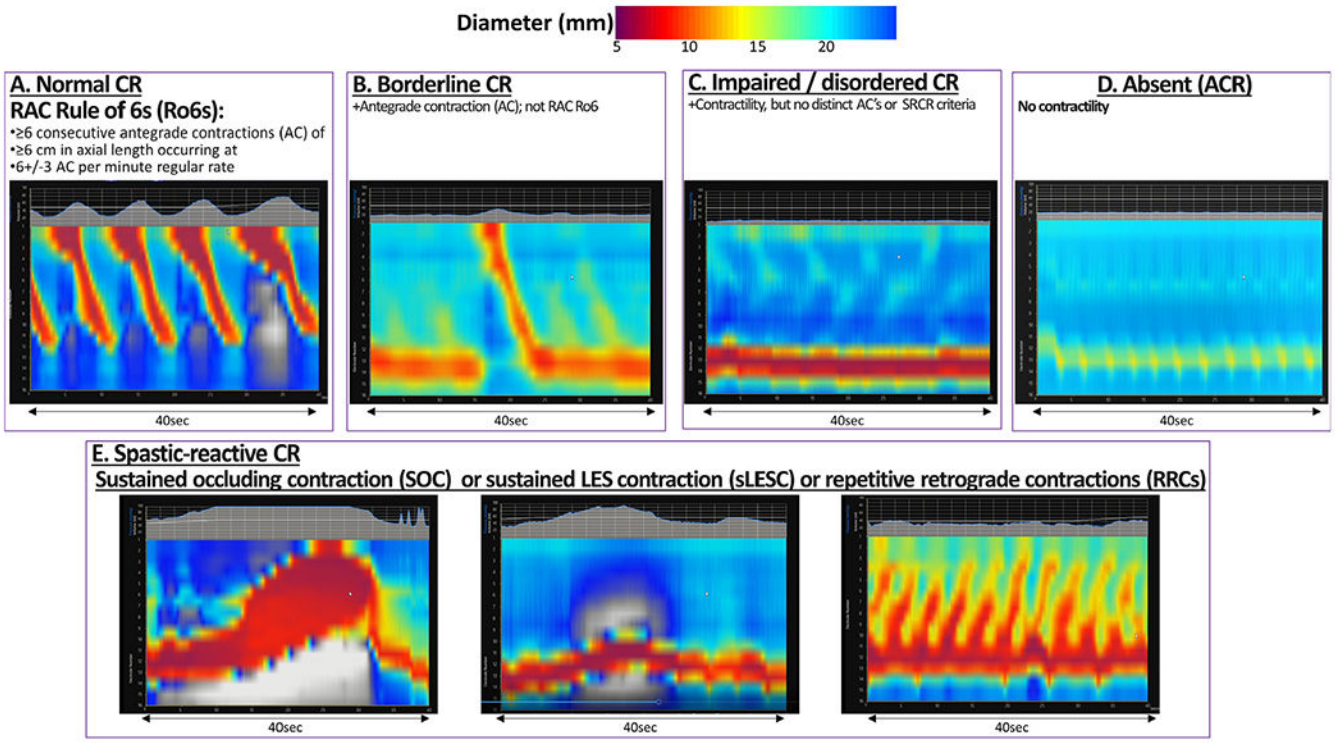

Figure 2.

Contractile response (CR) patterns observed in FLIP Panometry. The topographic images are of time (x axis), position along the probe (y axis) and luminal diameter (color). Hence, contractions appear much as they do in HRM with the distinction being that it is luminal diameter rather than pressure that is being portrayed. The normal CR (A) is of repetitive antegrade contractions (RACs) observed at some time during the 50, 60, or 70 mL distention volumes, each of which is maintained for at least 60 seconds. With a borderline CR (B), antegrade contractions are observed but not meeting RAC criteria. With an impaired/disordered CR (C), contractions are observed but without any distinct antegrade contractions. No contractility is observed with absent CR (D) usually seen with non-spastic achalasia or an HRM pattern of absent contractility. With the spastic/reactive CR (E) sustained occluding contractions (SOC), sustained LES contraction (sLESC), or repetitive retrograde contractions (RRCs) are seen, any one of which constitutes a spastic reactive CR. Figure used with permission from the Esophageal Center at Northwestern.

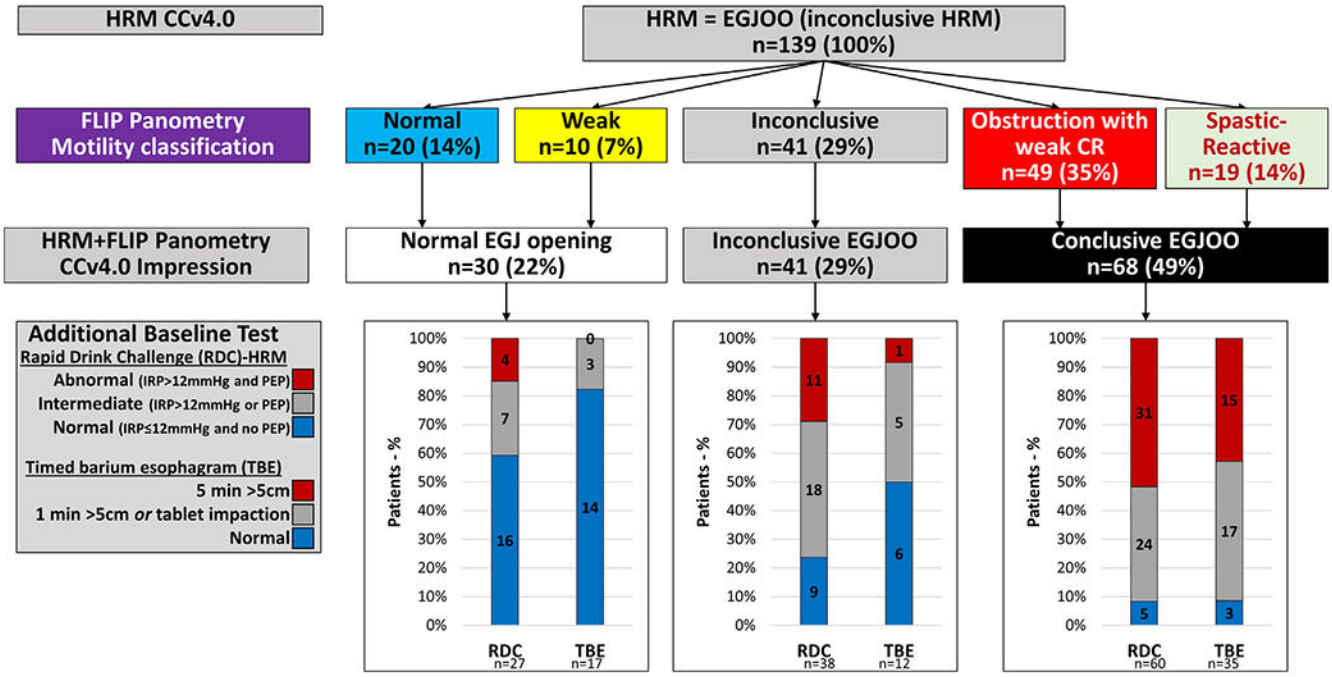

Figure 3.

Results of further evaluation of EGJ outflow obstruction (EGJOO) obstruction patients using provocative maneuvers, FLIP panometry, and timed barium esophagram (TBE) as proposed in Chicago Classification v4.0. Initially, all EGJOO diagnosed are considered inconclusive but with the addition of FLIP panometry 49% became conclusive and 22% were deemed normal, leaving 29% still inconclusive. Note that while all of the patients had both HRM and FLIP panometry only a portion of them had TBE and the rapid drink challenge (RDC) as indicated in the Figure. The associated finding from RDC and TBE are shown to emphasize the value of complimentary testing and the potential for inconsistency in diagnosis among testing modalities. PEP, panesophageal pressurization. Figure used with permission from the Esophageal Center of Northwestern.

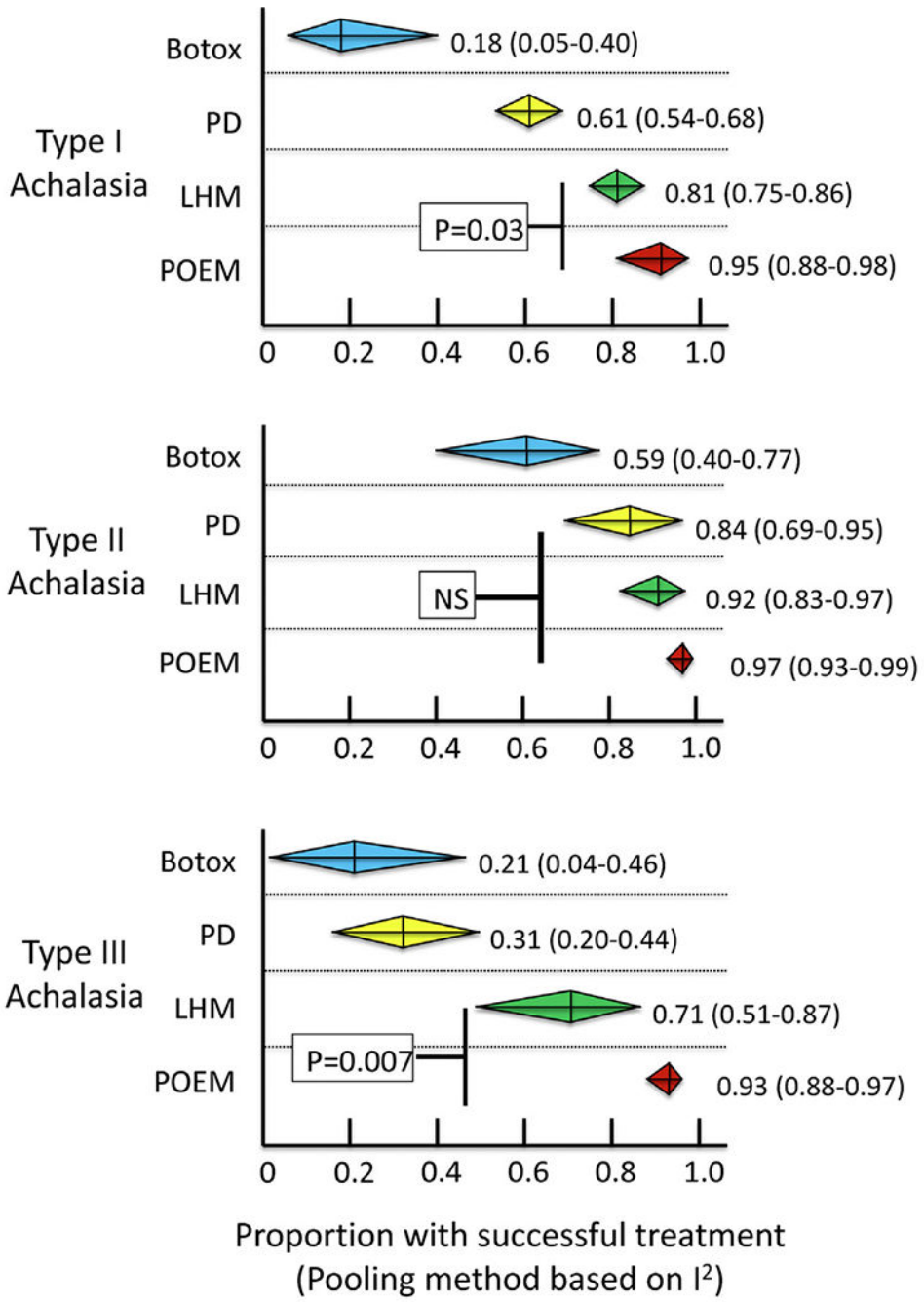

Figure 4.

Meta-analysis of studies reporting clinical outcomes of achalasia patients that were classified by manometric subtype after treatment with botulinum toxin injection, pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), or per-oral endoscopic myotomy (POEM). The major conclusions from the meta-analysis were that: (1) POEM was more successful than LHM for both type I (OR 2.97, $P = .03$) and type III achalasia (OR 3.50, $P = .007$), (2) POEM was the most efficacious treatment across the entire achalasia spectrum with pooled response rates of 95% 97% and 93% for type I, II, and III achalasia,

respectively, (3) PD had a lower but not significantly different success rate compared with POEM or LHM in type II achalasia, and (4) botulinum toxin injection was inferior in all subtypes. Data from Andolfi C and Fisichella PM, 2019.[4]