The Role of Novel Functional Probes in the Evaluation and Treatment of Esophageal Disease

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KEYWORDS

- Esophageal physiology • Gastroesophageal reflux disease • GERD • Achalasia
- Eosinophilic esophagitis • Functional lumen imaging probe • Mucosal impedance • Manometry

KEY POINTS

- Effective treatment of esophageal disease relies on a multifaceted evaluation of esophageal anatomy, physiology, and histology.
- The functional lumen imaging probe (FLIP) and mucosal impedance (MI) catheter are two novel technologies that can be used to evaluate esophageal function in a variety of disease states.
- FLIP uses impedance planimetry to measure the esophageal anatomy and determine the distensibility index (ie, resistance of the esophagus and esophagogastric junction to radial stretch).
- MI directly measures the impedance to electrical current through the esophageal mucosal surface. MI has been found to correlate with dilated intercellular spaces and other histologic changes caused by esophageal disease.

INTRODUCTION

The history of the treatment of esophageal disease over the last 100 years has been marked by technological advances that have greatly improved both diagnostic capabilities and the efficacy of therapeutic interventions. Advances in radiology, including contrast esophagram, CT, and PET, have allowed for a more granular assessment of esophageal anatomy and accurate detection and staging of malignant disease. In the late 1960s and 1970s, the development and rapid proliferation of flexible endoscopy radically altered the landscape of diagnosis and treatment of both benign and malignant esophageal disease.[1] Not only could the entire lumen of the esophagus and stomach be easily and safely visualized for assessment of anatomy and pathology but endoscopically based interventions could also be performed. Therapies, such as varied percutaneous endoscopic gastrostomy tube placement for feeding access, radiofrequency ablation for dysplastic Barrett esophagus and early cancer, band ligation of esophageal varices, and per-oral endoscopic myotomy (POEM) for achalasia, have dramatically reduced the invasiveness and morbidity of the treatment of these diseases.

The use of sensors and probes has also greatly enhanced our understanding of esophageal physiology and disease, and allowed for the accurate and objective diagnosis of a range of conditions. The introduction of conventional, and then high-resolution, manometry (HRM) allowed for the

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scientific study of esophageal physiology and the nuanced diagnosis of a range of esophageal motility disorders, including achalasia.[2] The development of the 24-hour pH-monitoring catheter by Johnson and Demeester[3] in the 1970s enabled the objective assessment of gastroesophageal reflux (GER), allowing for a more precise and effective utilization of both medical and surgical therapies. The introduction of a wireless pH monitoring probe further reduced the patient discomfort associated with testing.[4]

In the past 10 years, the development and study of 2 novel esophageal measurement probes has further added to the armamentarium of clinicians evaluating and treating patients with esophageal disease. The functional lumen imaging probe (FLIP) and mucosal impedance (MI) catheter both use electrical impedance measurements to objectively assess properties of esophageal anatomy, physiology, and even histology. This review serves as an introduction to these two measurement devices and discusses the current evidence supporting their use in the diagnosis and treatment of a variety of esophageal diseases.

FUNCTIONAL LUMEN IMAGING PROBE

Functional Lumen Imaging Probe Technology

FLIP is a catheter-based device that is inserted transorally, usually with patients under moderate sedation or anesthesia in the setting of an upper endoscopy or surgical procedure. The distal end of the catheter shaft contains 16 electrode pairs spaced at fixed intervals (ranging 5–10 mm in current commercially available models [Crospon; Galway, Ireland]) over a span of 8 cm or 16 cm (**Fig. 1**). The segment of the catheter that contains these electrodes is housed within an infinitely compliant plastic bag that can be variably inflated with saline solution using the device controls. Excitation electrodes at either end of the catheter emit a continuous low electric current, and impedance planimetry measurements are taken between each of the electrode pairs. These measurements are translated to cross-sectional areas (CSAs) at the level of each electrode pair using Ohm's law. These CSAs can then be combined to create a graphic representation of luminal anatomy that can be viewed in real time on the device display (**Fig. 2**).[5] A solid-state sensor measures pressure within the bag. FLIP has been most commonly used to measure the anatomy and function of the lower esophageal sphincter (LES) and esophageal body; but studies assessing its use for the upper esophageal sphincter, sphincter of Oddi, and anal sphincter have also been performed.[6–8] The most-studied FLIP measure of LES physiology is distensibility index (DI), which is calculated by dividing the minimum CSA (ie, narrowest point of the LES) by intrabag pressure. More recent studies have graphed CSA measurements (y-axis) over time (x-axis) to create FLIP topography plots, similar to the pressure topography plots used to display and analyze HRM measurements (**Fig. 3**). These topography graphs have enabled the use of FLIP to detect normal and abnormal esophageal contractions that occur in response to the volumetric distention caused by FLIP bag inflation, and represent a novel method for assessing esophageal motility.

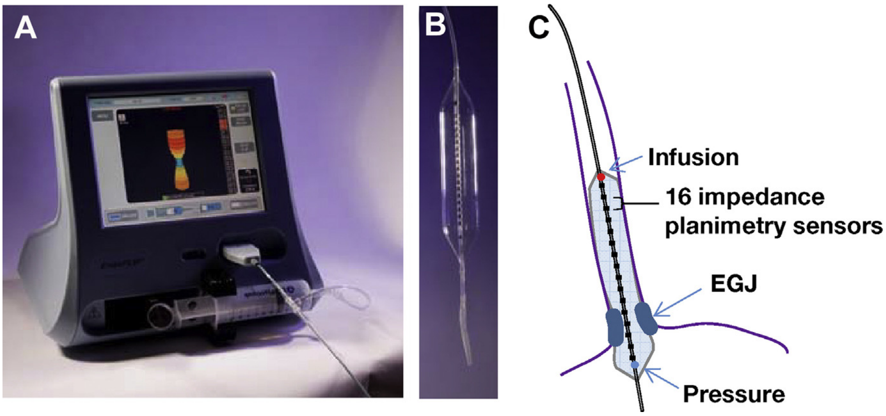

Fig. 1. The FLIP device and control console display (*A*) a graphic representation of esophageal lumen geometry. (*B*) A photograph and (*C*) cartoon of the FLIP measurement catheter are shown. The tip of the catheter contains 16 impedance planimetry electrodes and a pressor sensor, housed within a variably inflatable bag into which saline solution can be infused. EGJ, esophagogastric junction. (*From* Hirano I, Pandolfino JE, Boeckxstanes GE. Functional lumen imaging probe for management of esophageal disorders: expert review from the clinical practice updates committee of the AGA Institute. Clin Gastroenterol Hepatol 2017;15(3):325–34; with permission.)

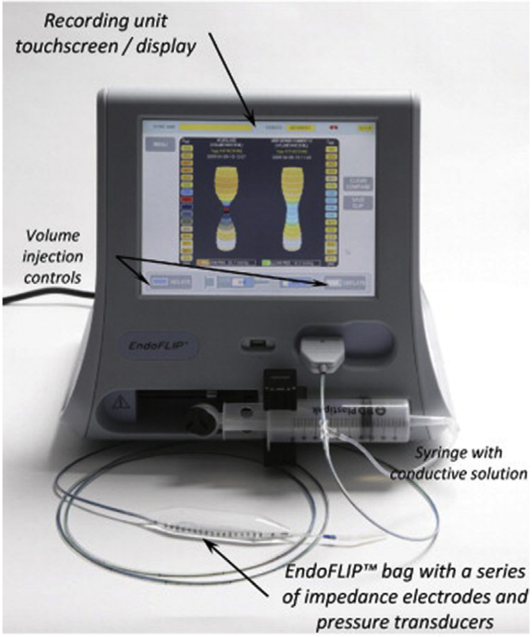

Fig. 2. The FLIP console displays a graphic representation of esophageal lumen geometry in real time as measurements are taken with the FLIP catheter. Touchscreen controls are used to variably inflate the FLIP catheter bag with saline solution. (*From* Kwiatek MA, Pandolfino JE, Hirano I, et al. Esophagogastric junction distensibility assessed with an endoscopic functional luminal imaging probe (EndoFLIP [Crospon; Galway, Ireland]). Gastrointest Endosc 2010;72(2):272–8; with permission.)

Achalasia

Achalasia is the most common primary esophageal motility disorder, resulting from an immune-mediated loss of esophageal inhibitory neurons. A resultant combined failure of LES relaxation and esophageal body peristalsis causes symptoms of dysphagia, regurgitation, chest pain, and weight loss.[9] Endoscopy is performed to rule out a mechanical source of obstruction, and the diagnosis is confirmed by HRM. Medical therapies are generally ineffective, and the mainstays of treatment are interventions designed to ablate the LES in order to allow for passive transit of food boluses into the stomach. Two such procedures, endoscopic pneumatic dilation and laparoscopic Heller myotomy, have been considered the standard of care for the past 20 years; a novel intervention POEM is rapidly gaining acceptance as a minimally invasive and durable alternative. Although HRM is considered the gold standard for the diagnosis of achalasia, less is known about the optimal evaluation of postintervention esophageal physiology. FLIP has recently been introduced as an additional means of assessing patients with achalasia before, during, and after interventions.

Two landmark studies established the use of FLIP as a diagnostic tool for assessing LES physiology in patients with achalasia.[10,11] Both studies focused on the use of FLIP in assessing the efficacy of interventions for achalasia. Pandolfino and colleagues[10] performed FLIP measurements in 4 patient groups: healthy controls, patients with achalasia before treatment, and 2 groups of patients with achalasia after treatment (with either pneumatic dilation or surgical myotomy), those with a good symptom response and those with persistent symptoms. As expected, patients with untreated achalasia were found to have a much lower DI (ie, a less distensible or tighter) LES than healthy controls. However, a more interesting finding was that patients with a good response to treatment had a DI that was almost as high as healthy controls, whereas patients with a poor treatment response had a DI on par with the untreated achalasics. Furthermore, DI measurements using FLIP were better correlated with objective symptom scores in posttreatment patients than esophagogastric junction (EGJ) resting or relaxation pressures measured by HRM. In other words, FLIP measurements served as a better objective assessment of posttreatment physiology in patients with achalasia. A study by Rohof and colleagues[11] produced similar results, demonstrating that patients with untreated achalasia had a significantly lower DI than healthy controls (0.7 vs 6.3 mm^2/mm Hg; $P<.001$) and that posttreatment patients with symptomatic relief had higher DIs than those with poor clinical outcomes (4.4 vs 1.6 mm^2/mm Hg; $P = .001$). As with the study mentioned previously, FLIP DI was found to be more closely correlated with symptomatic outcomes than HRM pressures. The main driver of this result was a subset of patients who had reduced LES pressures after intervention but a poor clinical outcome. In these patients the DI was pathologically low, demonstrating the superiority of FLIP to HRM in the physiologic evaluation of patients with achalasia after pneumatic dilation or myotomy (Fig. 4). These studies established the use of FLIP in assessing outcomes after interventions for achalasia.

Based on this work, subsequent studies tested the utility of using FLIP as a measurement tool at the time of interventions for achalasia. The group at Northwestern University showed the feasibility of such assessments during both laparoscopic Heller myotomy and POEM procedures.[12] During this study, real-time FLIP measurements were performed during both procedures, showing a

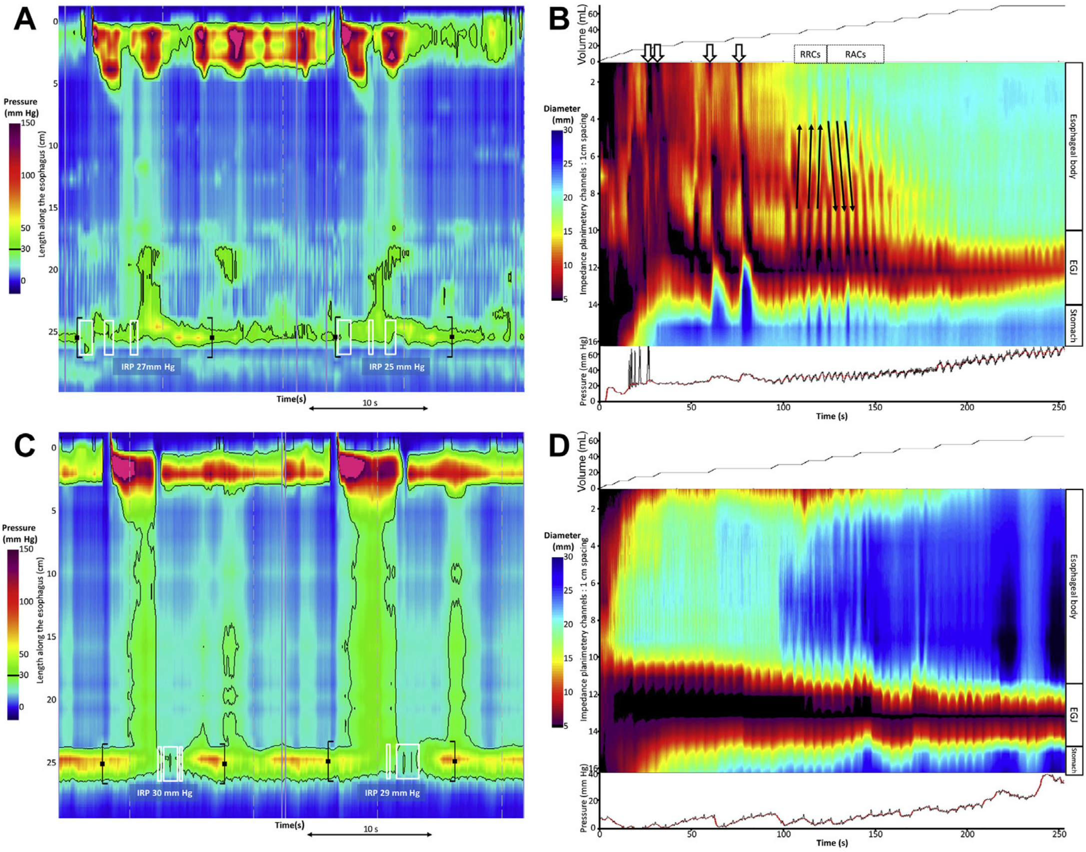

Fig. 3. FLIP topography plots can be created by graphing the length of the esophagus on the y-axis and time on the x-axis, with color representing luminal cross-sectional areas. These plots are similar to pressure topography plots (*A*) created using HRM. FLIP topography can be used to assess esophageal body motility (*B*) and can detect repetitive antegrade contractions (RACs) and repetitive retrograde contractions (RRCs) that are not seen on HRM (*C*). A FLIP topography plot (*D*) in a patient with type II achalasia shows an absence of RACs or RRCs. EGJ, esophagogastric junction. (*From* Carlson DA, Lin Z, Kahrilas PJ, et al. The functional lumen imaging probe detects esophageal contractility not observed with manometry in patients with achalasia. Gastroenterology 2015;149(7):1742–51; with permission.)

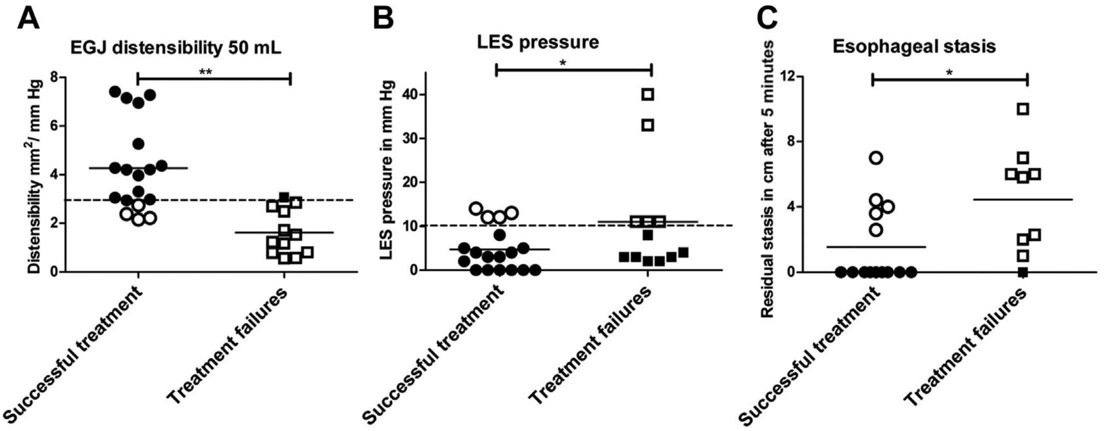

Fig. 4. In a study by Rohof and colleagues,[11] EGJ distensibility (*A*) as measured by the FLIP was better able to differentiate between patients with resolution and persistence of symptoms after procedural treatments for achalasia than either LES pressure on manometry (*B*) or esophageal stasis on esophagram (*C*) *Asterisks* denote *P*<.05. (*From* Rohof WO, Hirsch DP, Kessing BF, et al. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. Gastroenterology 2012;143(2):328–35; with permission.)

dramatic increase in DI as a result. Additionally, DI was assessed after each substep of these interventions (**Fig. 5**). During POEM, the steps of submucosal tunnel creation and myotomy were shown to both result in independent increases in DI. During laparoscopic Heller, performing the myotomy greatly increased DI (from a mean of 1.3 to 5.2 mm^2/mm Hg; $P<.001$), whereas subsequent creation of a partial fundoplication lowered DI (from 5.2 to 3.9 mm^2/mm Hg; $P<.01$). These results provided the first support for the use of FLIP as an intraoperative calibration tool. Theoretically, DI measurements could be used to ensure that adequacy of the myotomy in increasing LES compliance. During Heller myotomy with partial fundoplication, FLIP could then be used to tailor the fundoplication to verify that an adequate antireflux barrier had been created without excessively tightening the EGJ, which could result in postoperative dysphagia.

This concept was expanded on in 2 later studies in which sequential FLIP measurements were performed as the myotomy was created in increments during Heller and POEM.[13,14] In the first study, a short myotomy across the LES was created from 2 cm proximal to the EGJ to 3 cm distal to the EGJ and onto the stomach. After an initial FLIP measurement was taken, the myotomy was extended proximally to a total of 6 cm proximal to the EGJ. Interestingly, this proximal extension was necessary to normalize DI during laparoscopic Heller myotomy, but the shorter myotomy confined to the LES was sufficient in POEM procedures.[13] A later study explored a similar question, this time extending the myotomy in an incremental fashion from proximal to distal during POEM procedures. These results showed that a myotomy across the LES and a further extension to 2 cm distal to the EGJ both increased DI significantly, whereas a subsequent extension to 3 cm distal to the EGJ did not further increase in DI.[14] During both of these studies there was a sizable degree of variability in DI measurements between individual patients at each of the operative time points. This finding suggests that rather than identifying an ideal myotomy length that applies to all patients, a better use of FLIP would be as a real-time calibration tool to tailor the proximal and distal myotomy length to each patient's unique physiologic requirements.

Based on the findings that DI correlates well with postintervention symptoms and FLIP can be used to measure DI in real time during laparoscopic Heller myotomy and POEM, subsequent research sought to establish whether intraoperative FLIP measurements can predict eventual clinical outcomes. During achalasia interventions, relief of symptoms, such as dysphagia and regurgitation, depends on successful ablation of the LES. However, if the compliance of the LES is increased too much, it could theoretically result in a higher incidence of postintervention iatrogenic GER. One study compared intraoperative FLIP measurements taken at the conclusion of both Heller myotomy and POEM procedures with outcomes in regard to both achalasia and GER symptoms.[15]

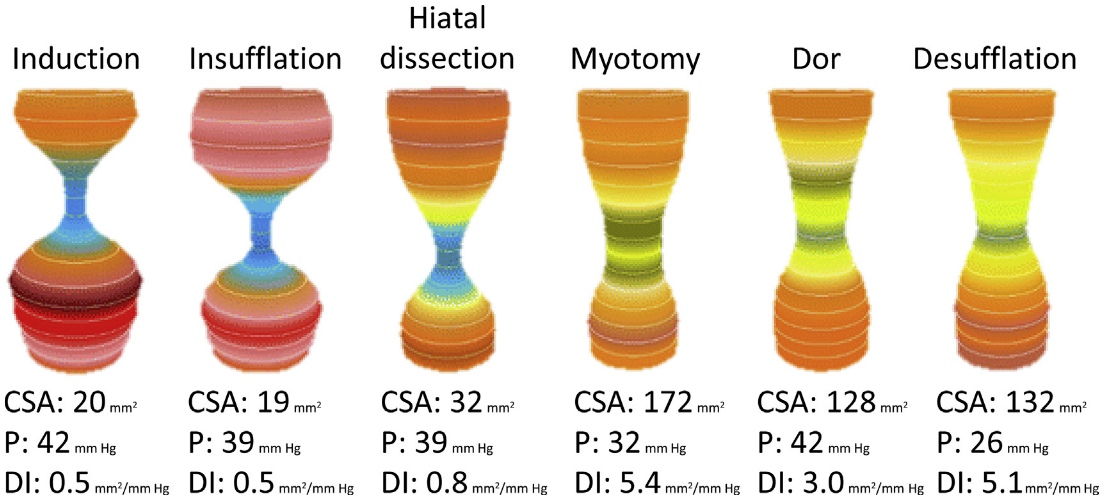

Fig. 5. FLIP measurements of CSA and intrabag pressure (Pres) are used to calculate EGJ DI after each step of a laparoscopic Heller myotomy with Dor fundoplication. A large increase in DI is seen after myotomy, and then a smaller decrease in DI occurs after creation of the Dor fundoplication. (*From* Teitelbaum EN, Boris L, Arafat FO, et al. Comparison of esophagogastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. Surg Endosc 2013;27(12):4547–55; with permission.)

During Heller myotomy, the only 2 patients with ending DI less than 3 both had poor symptomatic outcomes; across all Heller patients, the final intraoperative DI correlated with postoperative achalasia symptoms, as measured by the Eckardt symptom score.[16] Additionally, patients with a higher final DI were more likely to go on to have symptoms suggestive of iatrogentic GER. Compiling these two results, the investigators were able to determine a sweet spot range of the final DI: 4.5 to 8.5 mm^2/mm Hg. Patients who ended their procedure within this ideal range had optimal outcomes (minimal achalasia and GER symptoms) in 88% of cases, as opposed to only 47% of patients whose final DI was either greater than or less than this range.

Another study by Ngamruengphong and colleagues[17] added evidence to the predictive validity of FLIP measurements taken during POEM for the treatment of achalasia. The investigators found that patients with superior relief of achalasia symptoms (defined as an Eckardt score <3) had a higher mean LES CSA as compared with those with poor clinical outcomes. Additionally, patients with reflux esophagitis on follow-up endoscopy had higher CSA. These data support the concept that during operations for achalasia, a certain distensibility threshold must be met in order to ensure adequate relief of dysphagia. Conversely, too high a final DI may predispose patients to postoperative GER and esophagitis. Using FLIP during such operations could potentially serve as a quality-control measure to evaluate DI as the procedure progresses and tailor the myotomy and fundoplication to ensure that each operation ends with a DI in the ideal range.

A related study has shown a similar relationship between postintervention DI and symptomatic outcomes in patients undergoing pneumatic dilation for the treatment of achalasia.[18] Wu and colleagues[18] performed FLIP measurements before and after dilation in 54 patients. In patients with an immediate symptomatic response to dilation, DI increased by a mean of 4.5 mm^2/mm Hg, whereas in patients without symptomatic improvement, there was no significant change in DI. When evaluated as a continuous variable, DI was highly predictive of the clinical response to dilation, with an area under the curve of 0.89. A DI increase threshold of 1.8 mm^2/mm Hg was predictive of a good clinical outcome with 87% accuracy. Although pneumatic dilation to a fixed diameter (ie, 30, 35, or 40 mm) does not allow for calibration using intraprocedure FLIP, postdilation DI could be used to prognosticate and predict the need for repeat dilations at larger diameters or consideration for transition to alternative interventions, such as laparoscopic Heller or POEM, in patients who do not achieve an adequate distensibility increase.

Although initial investigations into the use of FLIP in patients with achalasia focused on its utility in the assessment of postintervention symptoms and measurement during these procedures, more recent studies have expanded the role of FLIP to the point of diagnosis. HRM measures LES pressures in response to swallowing and esophageal body contractility, and abnormalities in both are required to establish a diagnosis of achalasia. The studies using FLIP described previously only examined its ability to evaluate the LES. More recent work has expanded FLIP measurements to assess esophageal body activity in response to distention, by using a FLIP catheter with a longer 16 cm impedance electrode array and bag, compared with the 8 cm catheters used in prior studies. In addition to measuring LES DI at set time points, FLIP measurements have been recorded longitudinally over time to create FLIP topography plots similar to the pressure topography plots (ie, Clause plots) used to display and analyze HRM measurements (**Fig. 6**).

Carlson and colleagues[19] used such a graphical analysis and observed that FLIP can detect motility of the esophageal body (both normal and pathologic) in addition to LES distensibility. In healthy controls, inflation of the FLIP bag results in forward propagating peristaltic waves, similar to those seen with swallowing on HRM (**Fig. 7**). These waves occur in clusters, and the investigators termed them repetitive, antegrade contractions (RACs). Conversely, in patients with achalasia (particularly type III) and other esophageal motility disorders, FLIP distension produces repetitive, retrograde contractions (RRCs), a finding without a correlate on HRM. By combining the findings of LES DI and esophageal body contractility (absent, RACs, or RRCs), FLIP can now be used to fully assess esophageal physiology in a way that may compliment HRM. When HRM and FLIP were compared in 145 patients with dysphagia, 95% of patients with an abnormal HRM also had a corresponding abnormal FLIP, including all patients with an HRM diagnosis of achalasia. However, in the patients with a normal HRM, 50% had an abnormality seen on FLIP topography. These findings were used to create an algorithm for the analysis of FLIP measurements (**Fig. 8**), similar to the way in which the Chicago Classification is used to categorize patients based on HRM.[2] If validated in future studies, this classification system using FLIP could go on to serve as a complement, or even an eventual replacement, to the use of HRM for the evaluation

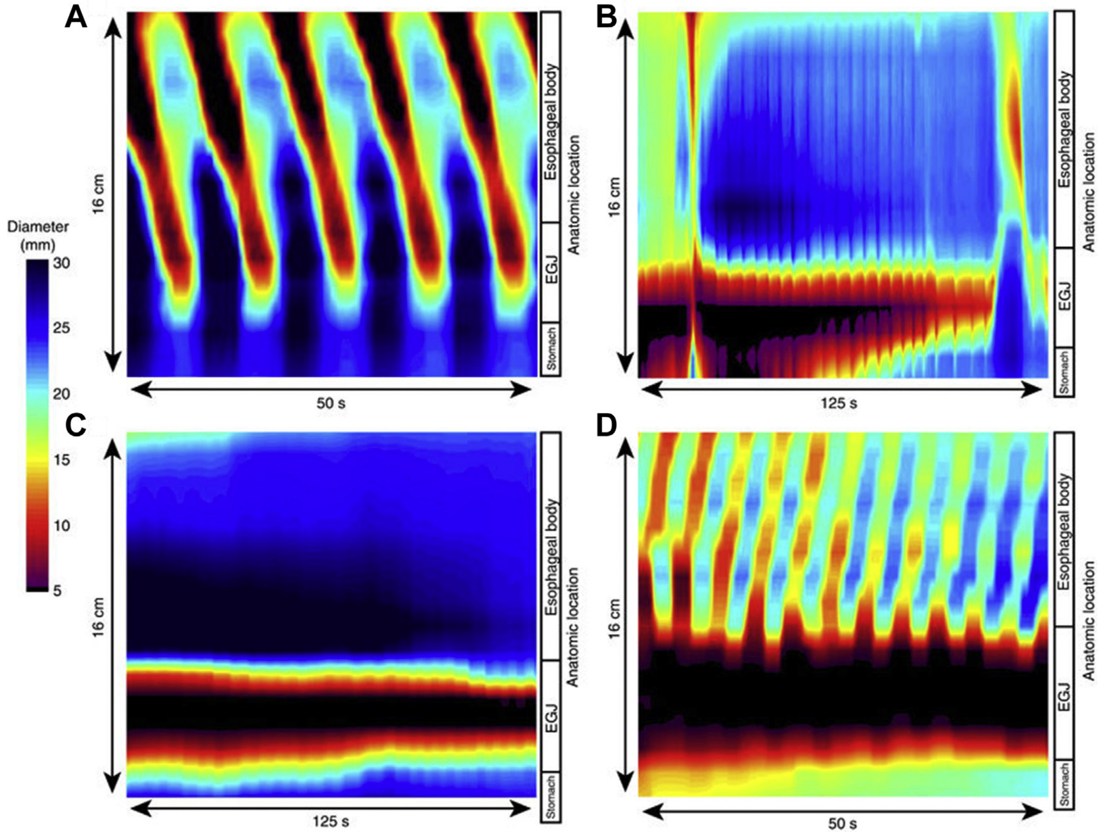

Fig. 6. Using FLIP topography plots, several patterns of esophageal body contractility can be observed. In asymptomatic controls, distention with the FLIP bag produces (*A*) repetitive, antegrade contractions (RACs). Patients with EGJ outflow obstruction with ineffective esophageal motility showed (*B*) esophageal contractility without RACs or repetitive, retrograde contractions (RRCs). Patients with type I achalasia typically have (*C*) elevated EGJ distensibility without any form of esophageal body contraction. Patients with type III achalasia often demonstrate (*D*) RRCs. (*Reprinted by* permission from Springer Nature. *From* Carlson DA, Kahrilas PJ, Lin Z, et al. Evaluation of esophageal motility utilizing the functional lumen imaging probe. The American Journal of Gastroenterology 2016;111:1726–35.)

and diagnosis of patients with nonobstructive dysphagia.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a food-allergen-driven immune-mediated disease of the esophagus that results in chronic eosinophil predominate inflammation.[20] Over time, this leads to fibrosis and stricturing of the esophageal body, causing symptoms of dysphagia and food impaction. Visual findings on endoscopy can be present, and the diagnosis is confirmed by identification of eosinophils on histology from esophageal biopsies. Treatment consists of a trial of gastric acid suppression with a proton-pump inhibitor (PPI) and, if unsuccessful, progression to topical steroids (ingested orally) and/or structured food elimination diets. Endoscopic dilation is used when fibrotic strictures occur as a result of longstanding inflammation. FLIP has recently been used to measure luminal distensibility and esophageal motility in patients with EoE and may serve as a useful adjunct measure in the diagnosis, prognostication, and assessment of treatment efficacy in such patients.

An initial study by Kwiatek and colleagues[21] evaluated FLIP measurements performed in 33 patients with EoE and 15 healthy controls. Not surprisingly, the patients with EoE were found to have a lower DI than the healthy controls; but interestingly, the histologic eosinophil count in the patients with EoE did not correlate with FLIP DI. A subsequent study of patients with EoE demonstrated that the severity of esophageal rings (ie, EoE strictures) was associated with lower distensibility as measured by FLIP (**Fig. 9**).[22] These findings suggest that FLIP is a measure of chronic

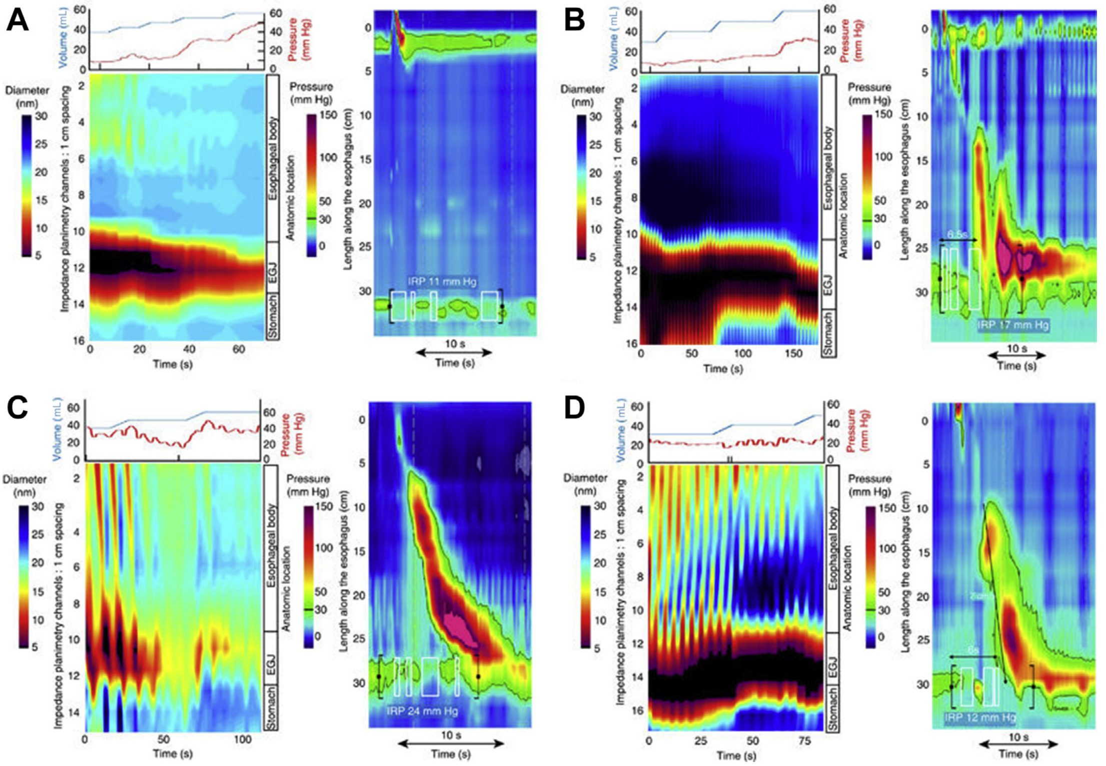

Fig. 7. FLIP topography plots were compared with HRM pressure topography plots in several patients. In a patient with type I achalasia FLIP topography (*A*) showed abnormal distensibility and absent contractility, whereas HRM had borderline relaxation pressure. In a patient (*B*) with esophagogastric outflow obstruction (EGJOO) but partially preserved peristalsis on HRM, FLIP showed elevated distensibility and no normal esophageal body contractility, suggesting a diagnosis of achalasia. Conversely, another patient (*C*) with EGJOO on HRM showed normal distensibility and repetitive, antegrade contractions on FLIP, making achalasia unlikely. Finally, a patient (*D*) with dysphagia had a normal HRM but elevated distensibility and repetitive, retrograde contractions on FLIP, suggesting that FLIP may be the more sensitive diagnostic test for esophageal motility disorders in certain patients. (*Reprinted by* permission from Springer Nature. *From* Carlson DA, Kahrilas PJ, Lin Z, et al. Evaluation of esophageal motility utilizing the functional lumen imaging probe. The American Journal of Gastroenterology 2016;111:1726–35.)

fibrosis and stricturing rather than acute inflammation in patients with EoE. Following from this, another study showed that FLIP measurements were able to predict the occurrence of food impaction and the need for endoscopic dilation during follow-up in patients with EoE.[23] In addition to prognostication, FLIP may be useful in evaluating the treatment effect in patients with EoE. A study by Carlson and colleagues[24] demonstrated that esophageal distensibility increased after initiation of EoE treatment (with topical steroids, food elimination diet, or PPI) without esophageal dilation. This finding suggests that although FLIP distensibility is primarily a measure of fibrosis and stricturing in patients with EoE, this fibrosis can potentially be remodeled as a result of medical or dietary therapy. If FLIP measurements are shown to be an effective objective marker of the efficacy of such treatments, it could replace the use of histologic analysis of multiple interval biopsies, which are costly and time consuming to obtain and evaluate.

Gastroesophageal Reflux Disease

GER disease (GERD) is an extremely common condition resulting from the failure of the mechanical barrier of the LES to prevent retrograde reflux of acidic gastric secretions into the esophagus.[25] It causes symptoms of heartburn and regurgitation and over time can lead to the formation of peptic strictures and the metaplastic conversion of esophageal squamous to intestinal columnar mucosa (ie, Barrett esophagus), which is a risk factor for the development of esophageal adenocarcinoma. Empiric treatment is often initiated based on symptoms alone, but 24-hour pH monitoring is the gold standard for establishing an objective diagnosis.

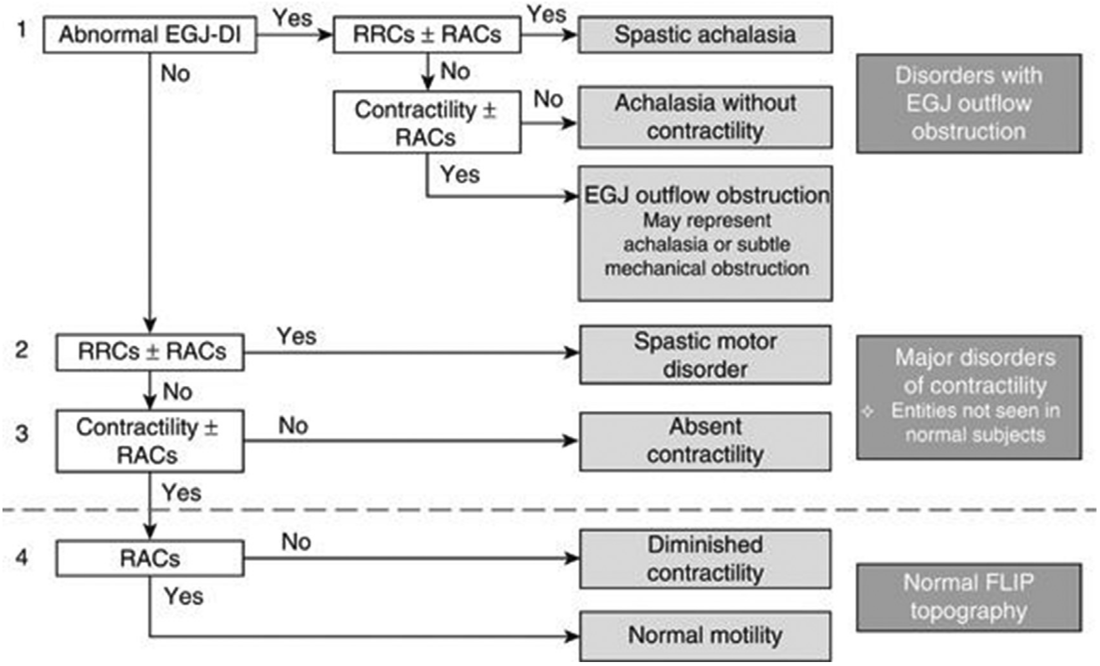

Fig. 8. A proposed algorithm for using FLIP topography to diagnose esophageal motility orders. EGJ-DI, EGJ distensibility. (*Reprinted by* permission from Springer Nature. *From* Carlson DA, Kahrilas PJ, Lin Z, et al. Evaluation of esophageal motility utilizing the functional lumen imaging probe. The American Journal of Gastroenterology 2016;111:1726–35.)

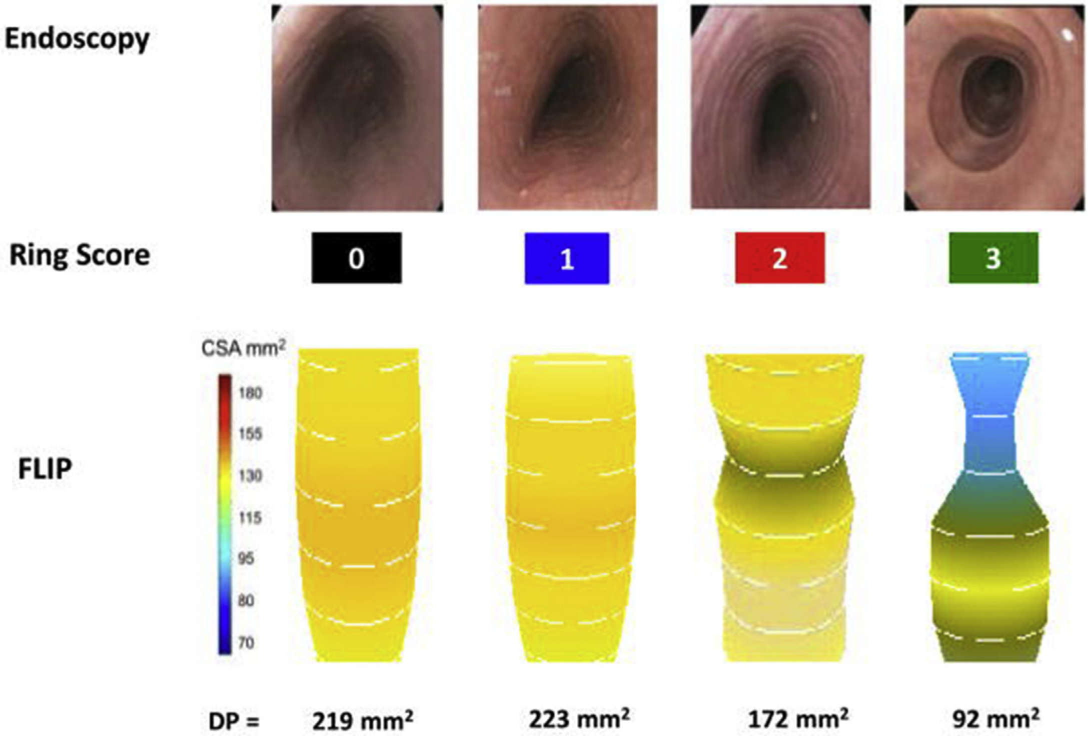

Fig. 9. In patients with eosinophilic esophagitis, distensibility as measured by the FLIP correlates with the severity of esophageal stenosis seen on upper endoscopy. *DP*, distensibility plateau. (*From* Chen JW, Pandolfino JE, Lin Z, et al. Severity of endoscopically identified esophageal rings correlates with reduced esophageal distensibility in eosinophilic esophagitis. Endoscopy 2016;48(9):794–801; with permission.)

Medical therapy with PPIs forms the mainstay of palliative treatment of GERD; surgical therapy, traditionally a laparoscopic fundoplication, is offered to patients who desire freedom from long-term medication dependence, have symptoms that are refractory to PPI therapy, or have complications of GERD, such as stricture, that develop or progress despite medical management. As LES functional integrity in the face of postprandial gastric distension is key to the prevention of GER, it follows that LES distensibility as measured by FLIP may be a valid metric in the evaluation of patients with GERD. Such research is still in its infancy; but there is reason to think that FLIP may serve as a valuable adjunct physiologic measure in the diagnosis, treatment, and post-intervention evaluation of patients with GERD.

In an early study by Kwiatek and colleagues,[5] FLIP measurements at the EGJ were performed in healthy controls and patients with symptoms consistent with GERD. The investigators found that the patients with GERD had a LES DI that was twice that of healthy controls (8 vs 4 mm^2/mm Hg; $P<.05$). The was no correlation between FLIP distensibility measurements and endoscopically visualized Hill grade[26] of the EGJ flap valve. This finding suggests that although FLIP has the capacity to measure the compliance of the LES, it does not detect all the anatomic aspects of the EGJ that contribute to the prevention of GER. Another study showed that after undergoing fundoplication for treatment of GERD, patients had lower DI than healthy controls.[27] This finding formed the basis for potential intraoperative use of FLIP in order to calibrate the fundoplication.

DeHaan and colleagues[28] performed such a study in which intraoperative FLIP measurements were taken in 2 sets of patients: those undergoing compete, 360° fundoplication (ie, Nissen fundoplication) and others during partial posterior fundoplication (ie, Toupet fundoplication). They found that Toupet fundoplication resulted in a higher (ie, less constricted) final DI. In prior studies, Toupet fundoplication has been shown to result in fewer postoperative symptoms of dysphagia and gas bloating when compared with Nissen.[29] The difference in FLIP distensibility between the two fundoplications raises the possibility that such intraoperative measurements could be used to calibrate wrap tightness in order to avoid postoperative dysphagia. However, further work is needed to correlate intraoperative FLIP measurements with postoperative symptomatic and physiologic outcomes in patients undergoing antireflux surgery before the technology can be applied during surgery on a routine basis.

MUCOSAL IMPENDENCE

Mucosal Impendence Technology

As opposed to FLIP, which uses impedance planimetry measurements to calculate interval CSAs in order to evaluate esophageal luminal anatomy, MI uses electrical tissue impedance spectroscopy technology to measure the surface bioelectrical properties of the esophageal mucosa itself. These measurements can evaluate histologic and functional aspects of the mucosa and its response to disease states. The MI probe is a narrow, flexible catheter that fits through the working channel of a standard gastroscope (**Fig. 10**).[30] Its tip contains impedance electrodes; when the probe is advanced to contact the esophagus, these electrodes measure the resistance to the flow of an electrical current passing between the electrodes across the mucosal surface.[31] MI can be altered by changes in mucosal histology, such as the presence of dilated intercellular spaces (DIS). Such DIS can form as a response to acid exposure in patients with GERD[32]; thus, MI may serve as an effective and efficient measure of the histologic response of the esophageal mucosa to GER and other disease states. The ability to perform MI measurements in real time during diagnostic and therapeutic upper endoscopy makes the technology an attractive alternative to costly, time-consuming, and/or uncomfortable diagnostic

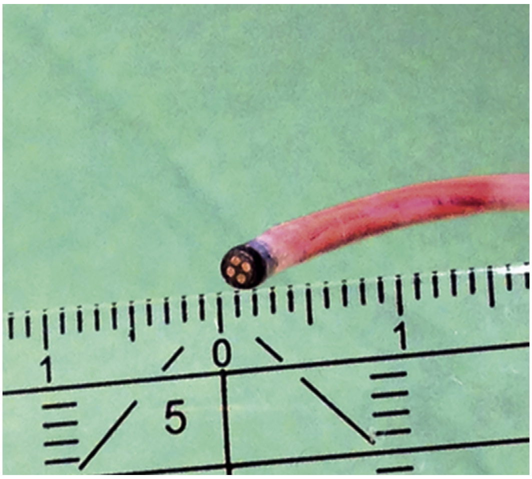

Fig. 10. The MI catheter fits through the working channel of a flexible gastroscope. Its tip, shown in this image, contains electrodes that measure tissue impedance when placed into contact with the esophageal mucosa. (*From* Weijenborg PW, Rohof WOA, Akkermans LMA, et al. Electrical tissue impedance spectroscopy: a novel device to measure esophageal mucosal integrity changes during endoscopy. Neurogastroenterol Motil 2013;25(7):57–8; with permission.)

tests, such as tissue biopsy histology and 24-hour pH monitoring.

Clinical Uses of Mucosal Impendence

Several early studies have laid the theoretic groundwork for the use of MI in the diagnosis and management of GERD and EoE. Saritas Yuksel and colleagues[33] performed MI measurements in patients with GERD confirmed by 24-hour pH monitoring and in healthy controls. They found that MI values at 2 cm proximal to the EGJ were lower in patients with GERD (2096 Ω vs 3607 Ω; $P<.01$). Additionally, in patients with GERD there was a gradient of MI that increased as the probe was moved from distal to proximal in the esophageal body. In the area of erosive esophagitis, the MI values were significantly lower than in noninflamed mucosa. Taken together, these results suggest that MI can detect mucosal changes resulting from GER and additionally grade the severity of those changes. In a subsequent study, MI measurements were compared with 24-hour pH monitoring results in their ability to predict the presence of erosive esophagitis on endoscopy. MI was found to have superior specificity and positive predictive values (95% and 96%, respectively) as compared with pH monitoring (64% and 40%), whereas the sensitivity and negative predictive values of the tests were similar.[34] If these results can be validated in future studies, MI could potentially supplant 24-hour pH monitoring as the test of choice for objective confirmation of the presence of pathologic GER because of its ease of application during diagnostic upper endoscopy.

Similar work has evaluated the utility of MI measurements in patients with EoE. Katzka and colleagues[35] performed endoscopic MI measurements and esophageal biopsies on 3 groups: healthy controls, patients with active EoE, and patients with inactive EoE. They found that MI was significantly lower in patients with active EoE (defined by >15 eosinophils per high-power field on biopsy) when compared with healthy controls and patients with inactive, or posttreatment, EoE. There was excellent overall correlation between MI and the number of eosinophils on biopsy; MI was able to distinguish between active and inactive disease with a sensitivity and specificity of 90% and 91%, respectively, using an impedance cutoff of 2300 Ω. Furthermore, MI correlated well with the degree of DIS seen on histology. These data suggest that although FLIP may be a surrogate marker of chronic fibrosis and stricture in patients with EoE, MI is able to detect active eosinophil-mediated inflammation. This finding supports the ongoing study, and potential future clinical use, of both FLIP and MI as complementary objective assessments in such patients to monitor disease progression and treatment response.

SUMMARY

A multifaceted evaluation of anatomy, physiology, and histology is essential to the medical and surgical treatment of esophageal disease. Technological advancements have allowed for a more nuanced assessment of each of these components of esophageal function, and this in turn has allowed for more targeted and effective therapies that are tailored to individual patients' specific conditions. The recent introduction of FLIP and MI into the armamentarium of the esophagologist has broadened the options for such evaluation and application of personalized medicine to the esophagus. Although further study is needed to validate the early results described in this review and more clearly define the role of these technologies in patient assessment, it is clear that FLIP and MI each offer a novel and exciting method to better understand esophageal function in normal and disease states.

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