Utility of Functional Lumen Imaging Probe in the Evaluation of Esophageal Conditions

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While often considered a newer physiologic tool in esophagology, endoluminal functional lumen imaging probe (FLIP) has been commercially available for nearly 15 years. Over this time, the utility of FLIP to evaluate patients with suspected esophageal motility disorders and to tailor interventions in patients with known foregut pathology has become increasingly established. In this review, we characterize the FLIP protocol and metrics and explore how FLIP is applied in clinical practice for various esophageal symptoms and conditions.

FLIP leverages 2 fundamental principles of esophageal physiology: esophagogastric junction (EGJ) distension, which occurs in response to intrabolus pressure and bolus passage during esophageal emptying, and peristalsis activated in response to esophageal distension or secondary peristalsis (1). FLIP evaluates these physiologic phenomena through impedance planimetry, which measures luminal diameter-pressure changes across a space-time continuum. The FLIP assembly consists of a distensible bag encasing a catheter with 16 pairs of impedance electrodes that is connected to a module, which includes a mechanical pump that volumetrically fills the bag with fluid (Figure 1). As the bag fills, FLIP measures luminal cross-sectional area (CSA) and distensive pressure in real time to enable the assessment of opening across the EGJ and esophageal contractile patterns in response to distension (1).

FLIP is typically performed during upper gastrointestinal endoscopy in a sedated patient. It is recommended to avoid sedatives that disrupt cholinergic properties such as ketamine, glycopyrrolate, and sevoflurane, among others. Furthermore, FLIP should not be used in the setting of actively bleeding esophageal varices, severe esophagitis, and active food impactions. FLIP is well tolerated, and adverse events using FLIP are rare, seldom including catheter malfunctions (see Supplemental Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C984).

When using FLIP in clinical practice, the catheter is placed transorally and advanced so that the bag traverses the EGJ. The 2 FLIP catheters available for clinical use include an 8-cm catheter with sensors spaced 0.5 cm apart or a 16-cm catheter with sensors spaced 1 cm apart (Figure 1). The 8-cm catheter provides high-resolution CSA and distensibility metrics and, for esophageal conditions, is positioned across the EGJ. The 16-cm catheter is positioned across the EGJ and extends proximally within the esophageal body, providing esophageal body contractility patterns in addition to EGJ metrics. The FLIP bag is initially filled to either 20 mL when using the 8-cm catheter or 30 mL using the 16-cm catheter to confirm appropriate placement across the EGJ and subsequently filled. The original protocol recommended filling in 10-mL increments from the initial fill volume until a target volume of 50 mL for the 8-cm or 70 mL for the 16-cm catheter is reached. The most vetted normative values for FLIP have been observed at a 60-mL volumetric distention using the 16-cm catheter (2,3). Wait periods of 30–60 seconds are recommended at each volumetric distention.

At the EGJ, FLIP measures CSA and pressure; this relationship of area and pressure provides a measurement of distensibility, termed the distensibility index (DI). Normal EGJ opening is defined as EGJ-DI $\geq$ 2.0 mm^2/mm Hg and a maximum EGJ diameter $\geq$16 mm (3). Reduced EGJ opening is defined as EGJ-DI $<$ 2.0 mm^2/mm Hg and a maximum EGJ diameter $<$ 12 mm. Values in between constitute borderline EGJ opening (3) (Figure 1). In clinical practice, reduced EGJ opening can support the diagnosis of a disorder of EGJ outflow (4), namely achalasia and EGJ outflow obstruction. In addition, mechanical obstructive processes such as esophageal stricture should be considered, particularly if esophageal diameter is $<$14 mm with a luminal diameter plateau within the esophageal body.

Impedance sensors in the esophageal body using the 16-cm catheter display esophageal body diameter changes over time, which represent secondary contractile patterns and can support diagnoses of esophageal dysmotility (3,5) (Figures 2 and 3). Normal contractile response is defined by repetitive antegrade contractions and the rule of 6s: $\geq$6 consecutive antegrade contractions of $\geq$6 cm in axial length occurring at 6 ($\pm$3) antegrade contractions per minute regular rate. Spastic-reactive contractile response is defined by the presence of sustained occluding contractions, sustained lower esophageal sphincter (LES) contractions, and/or repetitive retrograde contractions (defined by at least 6 consecutive retrograde contractions occurring at a rate of $>$9 contractions per minute) (3). Absent contractile response is apparent when there is no contractile activity in the esophageal body. Borderline contractile response is characterized by distinct antegrade contractions of at least 6 cm axial length; however, not meeting the rule of 6s criteria for repetitive antegrade contractions. Last, impaired/disordered contractile response may present as sporadic or

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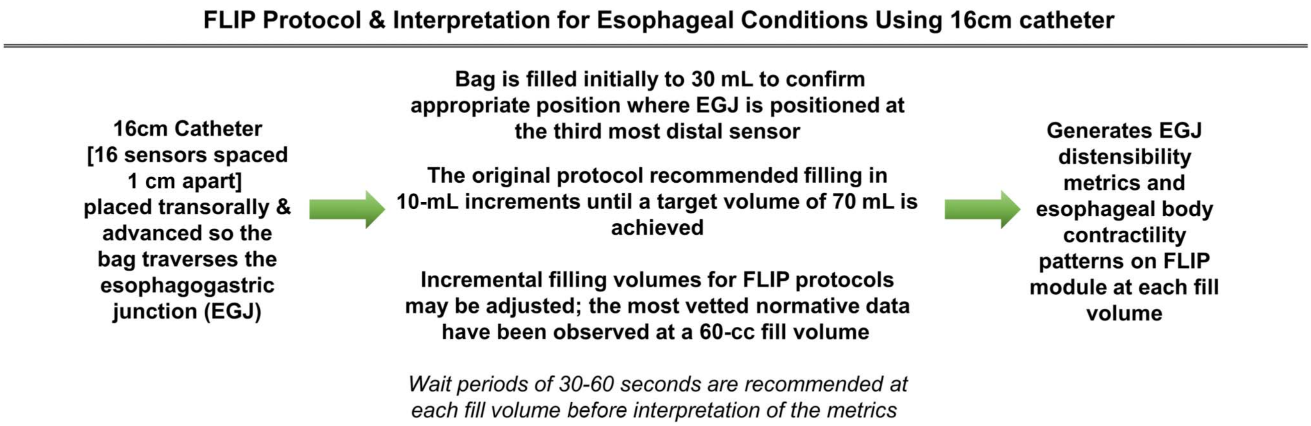

EGJ Function at 60mL fill volume	EGJ DI (mm^2/mm Hg)	EGJ Diameter (mm)
Normal Opening	≥ 2.0	≥ 16
Borderline Normal Opening	< 2.0	≥ 16
Borderline Reduced Opening	< 2.0	< 14
Reduced Opening	< 2.0	< 12

Esophageal Contractile Response	Contractile Pattern in Esophageal Body
Normal Contractile Response	Repetitive antegrade contractions (RAC)
Borderline Contractile Response	Distinct antegrade contractions not meeting criteria for RAC
Impaired/Disordered Contractile Response	Sporadic/chaotic contractions not meeting criteria for antegrade contractions or SRCR
Absent Contractile Response	No contractile activity
Spastic-Reactive Contractile Response (SRCR)	Sustained occluding contractions and/or repetitive retrograde contractions

Figure 1. FLIP protocol and metrics. Standard FLIP protocol is detailed for the 16-cm catheter, which provides both esophageal body contractility patterns and EGJ metrics. EGJ metrics at a 60-mL fill volume are highlighted in the bottom left table with corresponding EGJ opening classifications. Normal EGJ opening is defined as EGJ-DI $\geq$ 2.0 mm^2/mm Hg and a maximum EGJ diameter $\geq$ 16 mm. Reduced EGJ opening is defined as EGJ-DI $<$ 2.0 mm^2/mm Hg and a maximum EGJ diameter $<$ 12 mm. Values in between constitute borderline EGJ opening. Esophageal contractile response classifications at a 60-mL fill volume and their corresponding contractile patters are highlighted in the bottom right table. Normal contractile response is defined by RAC. Borderline contractile response is defined by distinct antegrade contractions not meeting criteria for RAC. Impaired/disordered contractile response is defined by sporadic/chaotic contractions not meeting criteria for antegrade contractions or SRCR. Absent contractile response is defined by no contractile activity. SRCR is defined by sustained occluding contractions and/or repetitive retrograde contractions. DI, distensibility index; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; RAC, repetitive antegrade contraction; SRCR, spastic-reactive contractile response.

chaotic contractions that do not meet criteria for antegrade contractions or spastic-reactive contractile responses (3).

DIAGNOSTIC UTILITY OF FLIP

FLIP at index endoscopy

Dysphagia is reported in approximately 1 in 6 adults and, in clinical practice, often presents with other esophageal symptoms (e.g., heartburn, regurgitation, noncardiac chest pain, odynophagia, and belching) (6). Heterogeneous and overlapping presentations lend to broad differentials for esophageal-related symptomatology, spanning gastroesophageal reflux disease (GERD) (erosive/nonerosive), eosinophilic esophagitis (EoE), esophageal motor disorders such as achalasia, or increasingly common disorders of brain-gut interaction, among others. In clinical practice, endoscopy is indicated as the first-line evaluation of esophageal dysphagia to determine the underlying etiology, exclude malignancy or premalignant conditions, and provide therapeutic intervention such as dilation (7). FLIP can be useful early in this diagnostic workup if available (Figure 4).

On index endoscopy, in the absence of obvious structural or mechanical etiology for esophageal dysphagia, FLIP may be considered to screen for an esophageal motility disorder. A normal FLIP (normal EGJ opening and normal contractile response in response to volumetric distention) has been demonstrated to have 92% positive predictive value for identifying normal motility on high-resolution manometry (HRM) (3). Thus, in the setting of a low pretest likelihood for a major motility disorder, a normal FLIP during index endoscopy may obviate the need for further evaluation with HRM or barium esophagram. On the contrary, studies have found that abnormal EGJ opening and absent contractility on FLIP predicts achalasia on HRM in 95% of patients (3). In this setting, FLIP during index endoscopy may facilitate expedited workup and perhaps real-time intervention (e.g., pneumatic dilation).

Diagnostic metrics for GERD on FLIP have been inconsistent (8,9). EGJ-DI has not consistently differed between abnormal and normal esophageal acid exposure time on ambulatory reflux monitoring (10). At this time, FLIP is not routinely recommended for GERD evaluation.

FLIP as supportive testing

In clinical practice, HRM is indicated for nonobstructive dysphagia (no mechanical etiology for esophageal dysphagia found on endoscopy) to evaluate for a primary esophageal motility disorder (4). However, certain patterns on HRM are not conclusive and require further evaluation with tools such as FLIP. These patterns include EGJ outflow obstruction because LES integrated relaxation pressure (IRP) can be elevated on HRM from etiologies other than a primary LES dysfunction. These etiologies include obscure mechanical stricture/angulation, hiatal hernia, and catheter artefact. Inconclusive findings for achalasia on HRM, such as high end of normal LES IRP in the setting of absent peristalsis, or when the LES

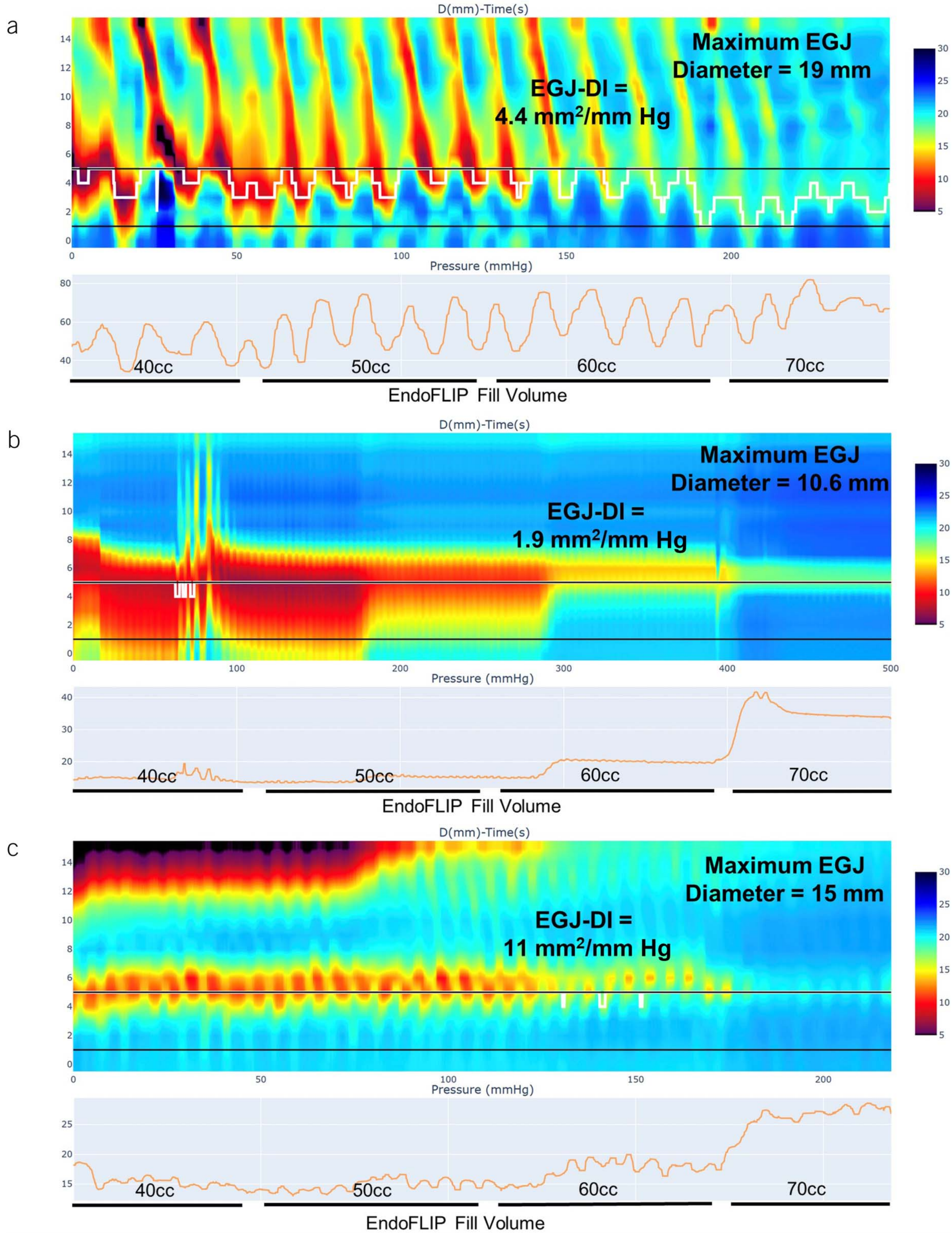

Figure 2. FLIP contractile patterns. FLIP panometry contractile response patterns are displayed for 3 unique patients (**a**–**c**) using the 16-cm catheter. The top panel displays color-coded FLIP topography plotted along length (16 cm) (y-axis) and time (x-axis). The bottom panel displays corresponding FLIP pressure. (**a**) Displays a patient with a normal CR with repetitive antegrade contractions and NEO; classified as normal FLIP panometry. This corresponded with normal esophageal motility on HRM. (B) Displays absent CR and reduced EGJ opening; classified as obstruction with weak FLIP panometry. This corresponded with type I achalasia on HRM. (**c**) Displays absent CR and NEO; classified as weak FLIP panometry. This corresponded with absent contractility on HRM. Courtesy of UCSD Center for Esophageal Diseases. CR, contractile response; DI, distensibility index; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; NEO, normal EGJ opening.

Contractile Response	Esophagogastric Junction (EGJ) Opening: Normal	Borderline Normal	Borderline Reduced	Reduced
Normal	>90% Normal 0% Achalasia	60%–90% Normal/IEM 10%–20% Major motor d/o 0% Achalasia	Consider Mechanical > 10% Major motor d/o	Consider Mechanical > 10% Major motor d/o
Borderline	>90% Normal/IEM 0% Achalasia	Inconclusive >60% Normal 5%–10% Achalasia >5% Major motor d/o		Inconclusive >30% Achalasia/Major motor d/o
Impaired/Disordered	60%–80% Normal 0% Achalasia 20%–30% IEM	Inconclusive 40%–50% Normal 20%–30% Achalasia		80%–90% Achalasia <5% Normal
Absent	50%–70% Absent/IEM 30%–50% Normal 0% Achalasia	50%–70% Absent/IEM 30%–50% Normal <5% Achalasia	80%–90% Achalasia < 5% Normal	> 90% Achalasia 0% Normal
Spastic Reactive	Inconclusive > 30% Achalasia/Major motor d/o			50%–80% Achalasia < 30% Normal

Figure 3. Relationships between patterns on FLIP and patterns on HRM. FLIP contractile patterns and EGJ opening classification are displayed with corresponding Chicago Classificationv4.0 (CCv4.0) HRM diagnoses. Each FLIP contractile pattern and EGJ opening classification permutation has the most likely corresponding HRM diagnosis underlined. In many instances, the contractile pattern and EGJ opening classification result in multiple possibilities of major motility disorders (d/o), in which case the corresponding overarching diagnosis is "inconclusive" and, in clinical practice, would require HRM to further characterize the disorder. A cold (blue) to hot (red) color scale is displayed, which demonstrates an overall likelihood of FLIP metrics corresponding to normal (blue) or achalasia (red) on HRM. Adapted from ref. (3). EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry.

IRP in upright and supine position are discordant, also require additional testing (4) (Table 1).

FLIP AS A GUIDE FOR TREATMENT

FLIP has a role in guiding foregut interventions and evaluating postintervention efficacy (Table 1). Intraprocedure EGJ-DI on FLIP can be measured during surgical Heller myotomy, per-oral endoscopic myotomy, or pneumatic dilation to assess adequacy of LES disruption (11–13). For example, in 1 study of cases with Heller myotomy and per-oral endoscopic myotomy, a post-myotomy EGJ-DI ≤ 3.1 mm²/mm Hg was significantly associated with treatment failure (11,12). FLIP can also help evaluate the

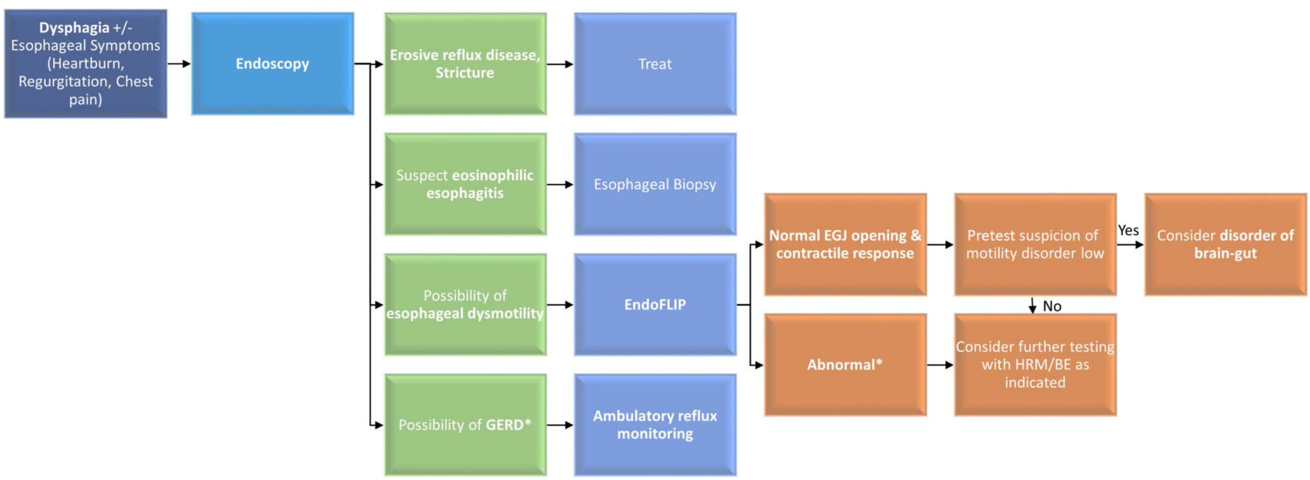

Figure 4. Diagnostic Capacity of functional lumen imaging probe on index endoscopy. A flow diagram of treatment and/or diagnostic testing based on findings during index endoscopy for the evaluation of dysphagia with or without other esophageal symptoms. *Normal EGJ opening with weak contractile response on EndoFLIP can be seen in GERD. BE, barium esophagram; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry.

Table 1. Roles for functional lumen imaging probe in clinical practice of esophageal conditions

Initial diagnostic tool	To evaluate nonobstructive dysphagia during an index endoscopy
Supportive diagnostic tool	To support a diagnosis of achalasia when HRM/BE is inconclusive for achalasia To support a diagnosis of EGJOO when HRM/BE is inconclusive for EGJOO
Guide for treatment adequacy	To assess the degree of posttherapy EGJ disruption in achalasia therapy (e.g., for surgical Heller myotomy, POEM, or pneumatic dilation) To tailor antireflux intervention
Prognostic tool	To assess fibrostenotic remodeling in patients with EoE

BE, barium esophagram; EGJ, esophagogastric junction; EGJOO, EGJ outflow obstruction; EoE, eosinophilic esophagitis; HRM, high-resolution manometry; POEM, per-oral endoscopic myotomy.

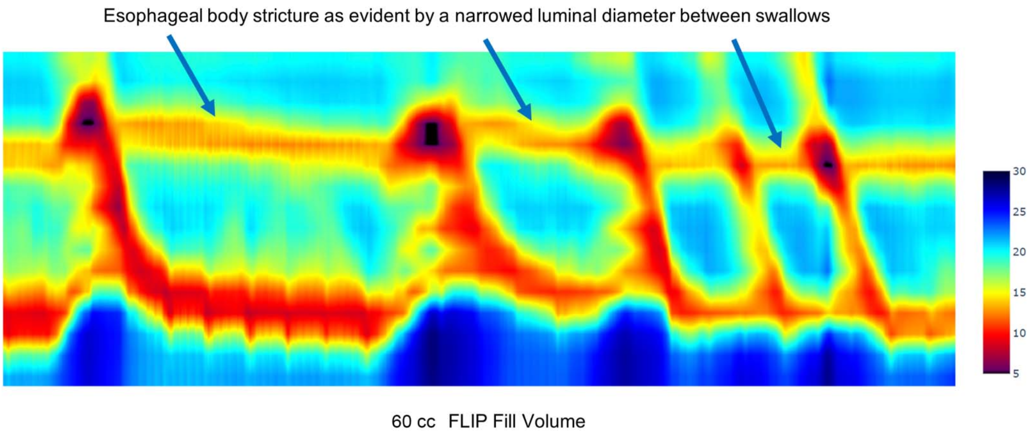

Figure 5. FLIP EoE example. FLIP pattern of a patient with EoE. This image represents 60 seconds of continuous FLIP monitoring at a 60-cc fill volume. An esophageal body stricture is demonstrated by a continuous line between swallows in the esophageal body where the lumen diameter is narrowed (blue arrows). Courtesy of Northwestern Center for Esophageal Diseases. EoE, eosinophilic esophagitis; FLIP, functional lumen imaging probe.

EGJ-DI after a fundoplication procedure, with EGJ-DI <2 mm^2/mm Hg associated with an increased risk of dysphagia and bloating (14). FLIP is being actively researched in magnetic sphincter augmentation and transoral incisionless fundoplication procedures.

Another area FLIP is being used and studied is in the management of EoE. In patients with pediatric EoE, luminal diameter on FLIP has been shown to negatively correlate with eosinophil density (15,16). Moreover, FLIP in patients with EoE, compared with control patients, suggests decreased compliance of the esophageal body and can predict need for dilation (15,16), occurrence of food impaction (15,16), and symptom improvement with dietary and/or pharmacologic therapy (17). A FLIP example image from a patient with EoE demonstrating an esophageal body stricture requiring dilation is provided in Figure 5.

CONCLUSION

Since its introduction 15 years ago, FLIP has become a standard physiologic tool used in endoscopy and surgery centers. FLIP has diagnostic utility as an up-front screening test or as a supportive test for major esophageal motility disorders. In addition, FLIP is being used in routine clinical practice to evaluate the completion and efficacy of foregut interventions.

CONFLICTS OF INTEREST

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