Published in final edited form as:

Neurogastroenterol Motil. 2016 December ; 28(12): 1844–1853. doi:10.1111/nmo.12888.

Evaluation of esophageal distensibility in eosinophilic esophagitis: An update and comparison of functional lumen imaging probe analytic methods

DA Carlson, Z Lin, I Hirano, N Gonsalves, A Zalewski, and JE Pandolfino

Department of Medicine, Division of Gastroenterology and Hepatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Abstract

Background—Distensibility evaluation of the esophageal body using the functional lumen imaging probe (FLIP) offers an objective measure to characterize patients with eosinophilic esophagitis (EoE), though this analysis may be limited by unrecognized catheter movement and esophageal contractility. The aims of this study were to report novel FLIP analytic methods of esophageal distensibility measurement in EoE and to assess the effect of contractility.

Methods—Nine healthy controls (6 female; ages 20 – 49) and 20 EoE patients (4 female; ages 19 – 64; grouped by degree of distension-mediated contractility identified on FLIP) were evaluated with a 16-cm FLIP device during step-wise balloon distension during upper endoscopy. A distensibility plateau (DP) was generated using multiple methods to identify the narrowest esophageal body diameter: 1) Wavelet decomposition (WD) 2) Maximal diameter (MD), and 3) FLIP Analytics software.

Results—Distensibility was reduced in EoE patients compared with controls using the WD ($p = 0.002$) and MD ($p = 0.001$) methods; a trend was detected using the FLIP Analytics method ($p = 0.055$). Significant intra-subject differences were detected between methods among both patients and controls (p -values $< 0.001 - 0.025$); the difference was more pronounced among subjects with a greater degree of contractility. DP was < 19 mm among 7/9 controls with FLIP Analytics, 6/9 controls with WD, and 0/9 controls using the MD-method.

Conclusion—Distension-mediated contractility affects distensibility measurement with the FLIP. Using software-based algorithms, particularly with a method that identifies the maximal

Corresponding Author: Dustin A. Carlson, MD, MS, Northwestern University, Feinberg School of Medicine, Department of Medicine, Division of Gastroenterology and Hepatology, 676 St Clair St, Suite 1400, Chicago, IL 60611-2951, dustin-carlson@northwestern.edu, Tel: 312-926-4939, Fax: 312-695-3999.

Disclosures:

John E. Pandolfino: Given Imaging (Consultant, Grant, Speaking), Sandhill Scientific (Consulting, Speaking), Takeda (Speaking), Astra Zeneca (Speaking)

Ikuo Hirano: Receptos, Inc (Consulting); Regeneron Pharmaceutical, Inc (Consulting), Shire (Consulting)

Nirmala Gonsalves: Nutricia (speaking)

Dustin A. Carlson, Zhiyue Lin, Angelika Zalewski: None

Author contributions: DAC contributed to study concept and design, data analysis, data interpretation, drafting of the manuscript, and approval of the final version. ZL contributed to data analysis, data interpretation, manuscript revision, and approval of the final version. AZ, IH, NG contributed to organization of data, recruitment of patients, and approval of the final version. JEP contributed to study concept and design, revising the manuscript critically, and approval of the final version.

achieved diameters (MD), may improve objective distensibility measurement for clinical research and practice.

Keywords

impedance planimetry; functional lumen imaging probe; eosinophilic esophagitis

Introduction

Eosinophilic esophagitis (EoE) is clinicopathologic disorder characterized by esophageal symptoms (commonly dysphagia and food impaction) and histologic evidence of eosinophilic inflammation.(1) The chronic inflammation in EoE is thought to progress to fibrostenotic changes manifested as the characteristic ringed and strictured esophagus that can result in esophageal mechanical obstruction and the resultant symptoms.(2)

The functional lumen imaging probe (FLIP) offers a unique evaluation of esophageal function by simultaneously measuring esophageal luminal cross-sectional area (often transformed to diameter) and distensive (i.e. intra-balloon) pressure during volume-controlled esophageal distension. The relationship between esophageal luminal dimensions and intra-balloon pressures, i.e. distensibility, has typically been quantified with FLIP via a metric termed the distensibility plateau (DP), which was conceptualized to reflect the fixed luminal diameter that would fail to expand despite increasing intra-balloon pressures.(3-5) Thus, the DP is derived by plotting the narrowest esophageal lumen diameter as a function of intra-balloon pressure obtained during step-wise, volumetric distension of the esophageal body. The DP was reported to be reduced in EoE patients compared with asymptomatic controls.(3) Further, among EoE patients, a greater reduction in DP was associated with the future risk for food impaction and/or requirement for therapeutic dilation.(5) Given the objectively measured and clinical relevance of distensibility assessment with the FLIP, FLIP-measured esophageal distensibility is a potential therapeutic target and outcome measure for therapeutic clinical trials, and ultimately, clinical practice.

However, there are some methodologic limitations related to distensibility measurements using the FLIP. Previous studies utilized an 8-cm FLIP device that was re-positioned proximally into the esophageal body after initial identification of the esophagogastric junction (EGJ).(3-5) However, the 8-cm FLIP method risks potential catheter movement within the esophageal body that may be difficult to recognize at the time of the study. Using the longer, 16-cm FLIP, the EGJ and distal esophageal body can be evaluated simultaneously, which allows for the EGJ to serve as an anatomical reference point during the FLIP study and analysis.(6)

Further, measurement of esophageal distensibility has typically relied upon the identification of the narrowest luminal diameter of the esophagus, which can be complicated by the dynamic nature of the FLIP study, particularly related to distension-mediated esophageal contractions and peristalsis complication. Esophageal contractility was handled in initial studies within the FLIP-study protocol (i.e. repeating measures when contractions occurred) and/or post-study data processing (particularly utilizing a wavelet decomposition (WD) filtering-mechanism).(3, 5) However, additional experience and observation of distension-

mediated contractility using FLIP topography, which represents distension-associated esophageal contractility in color-coded diameter by time by axial length plots (Figure 1), has increased appreciation for the extent of contractility-induced artifact and further, that the WD-filtering method may still be susceptible to contractile-associated luminal diameter changes in misrepresenting the narrowest fixed stenosis-related diameter.(7, 8)

Given these issues, we sought to refine and improve our assessment of esophageal body distensibility utilizing the 16-cm FLIP. Additionally, we hypothesized that subjects with a greater degree of esophageal contractility would demonstrate a greater susceptibility to variation in distensibility measures between analytic methods. Thus, the aims of this study were to report novel analytic methods incorporating the 16-cm FLIP and to also compare analytic methods of esophageal distensibility measurement in EoE.

Methods

Subjects

Consecutive, adult patients with EoE with esophageal eosinophilia (defined by ≥ 15 eosinophils/hpf) at the time of upper endoscopy with FLIP were included. Patients had presented to the Esophageal Center of Northwestern between October 2013 and April 2015 for evaluation of esophageal symptoms and were diagnosed with EoE per consensus guidelines with ≥ 15 eosinophils/hpf on esophageal biopsies after at least 8-weeks of proton-pump inhibitor (PPI) therapy.(1) Patients' symptoms at the time of endoscopy with FLIP were assessed using a validated, patient-reported outcome measure which ranged from 0 – 100; greater values indicated more severe symptoms.(9) EoE-related therapy (PPI, topical steroid, or elimination diet) at the time of evaluation was also recorded. To evaluate the effects of esophageal contractility on distensibility analysis, FLIP studies were analyzed for contractility, as described below, to allow for blocked-inclusion of 10 EoE patients with repetitive, antegrade contractions (RACs; representing a patient group with a greater degree of distension-mediated contractility) and 10 EoE patients without RACs (lesser degree of contractility).

Ten asymptomatic, healthy volunteers (controls; ages 20-49; 6 female) were also included. These subjects have been previously described.(6, 7) None of the controls had a history of malignancy or gastrointestinal surgery or endoscopic evidence of hiatal hernia, esophagitis, stricture, and/or mucosal changes suggestive of eosinophilic esophagitis. Informed consent was obtained from each subject. The study protocol was approved by the Northwestern University institutional review board.

Functional lumen imaging probe system and study protocol

The FLIP assembly consisted of a 240-cm long, 3-mm outer diameter catheter with an infinitely compliant balloon (up to a distension volume of 60 mL) mounted on the distal 18 cm of the catheter (EndoFLIP®; Crospon, Inc, Galway, Ireland). The balloon tapered at both ends to assume a 16-cm long cylindrical shape in the center that housed 17 impedance planimetry ring electrodes spaced at 1 cm intervals and a solid-state pressure transducer positioned at the distal end to provide simultaneous measurement of 16 channels of cross-

sectional area (which was converted to diameter based on the assumption of circular lumen cross-sections) and intra-balloon pressure. For simplification, impedance planimetry measurements will be reported as *diameter* for the remainder of this report. The impedance planimetry segment had a range of measureable diameters of 5.2 - 22 mm within the infinitely compliant limits of the balloon. Pressure values when the balloon was distended above 22-mm diameter could be measured, but mechanical properties of the balloon would be engaged and could contribute to pressure-generation above this distension range. Measurements from the impedance planimetry electrode pairs and the pressure transducer were sampled at 10 Hz with the data acquisition system and transmitted to the recording unit.

Subjects underwent upper endoscopy in the left lateral decubitus position. Moderate sedation with 2-12 mg midazolam and 0-250 µg fentanyl was administered during the procedure. The FLIP was pressure-zeroed to atmospheric pressure and then the probe was placed trans-orally and positioned with the distal 1-3 impedance sensors beyond the EGJ as confirmed by demonstration of a waist in the impedance planimetry segment at a balloon distension volume of 20-30 ml. The endoscope was withdrawn before initiation of the FLIP study protocol. The FLIP assembly position was adjusted by the endoscopist during the study to maintain placement relative to the EGJ as visualized on real-time output. Simultaneous diameters and intra-balloon pressures were measured during 5-ml step-wise distensions beginning with 5 ml and increasing to target volume of 60 ml. The recording unit was set to stop infusing and display an alarm message if the intra-balloon pressure exceeded 60 mmHg, which sometimes limited the extent of balloon distension; in these cases, the maximal distension volume achieved was recorded. Each step-wise distension volume was maintained for 20-30 seconds during a single distension protocol for each patient.

Endoscopic features of EoE (edema, rings, exudate, fissures, and stricture) were graded during the upper endoscopy according to the Endoscopic EoE Reference Score (EREFS). (10) If a stricture was present, the estimated luminal diameter was also reported. The endoscopy and FLIP study were performed by the same gastroenterologist, thus the real-time FLIP measures may have influenced the stricture size estimate. Therapeutic dilation was performed at the discretion of the treating endoscopist. Following the FLIP evaluation, esophageal mucosal biopsies were obtained from the distal (5-cm above the EGJ) and proximal (15-cm above the EGJ) for histologic evaluation and quantification of esophageal eosinophilia; the peak eosinophil count was reported.

Data analysis

Data including distension volume, intra-balloon pressure, and 16 channels of diameter measurements for the entire study for each subject were exported to MATLAB (The Math Works, Natick, MA, USA) for analysis using a customized MATLAB program. This program applied a filter to minimize vascular and respiratory artifact and then generated tracings of each channel's measured luminal diameter. Interpolation of each channels' diameter measurement was applied to generate color-coded topography plots with corresponding plots of volume distension and intra-balloon pressure by time (Figure 1).

Esophageal body contractions were identified by a transient decrease of 5 mm in the measured luminal diameter detected in 2 consecutive axial impedance planimetry channels using the FLIP topography plots and 16 channel diameter tracing output.(7, 8) Propagation direction was determined by the slope of the tangent line placed on the onset of contraction. RACs were considered when 3 antegrade (positive slope) contractions occurred consecutively and repetitive, retrograde contractions were considered when 3 retrograde (negative slope) contractions occurred consecutively.

Multiple methods were utilized to generate measures of esophageal body distensibility, which then formed the basis for intra-subject comparison. A distensibility plateau (DP) was generated using customized MATLAB programs via two methods that differed regarding identification of the narrowest esophageal body diameter during step-wise distension: 1) *wavelet decomposition* (WD), as with previously published results that utilized an 8-cm FLIP but adjusted to the 16-cm FLIP,(4, 5) and 2) a novel method using the *maximal-diameter* (MD) achieved for each impedance planimetry channel. For both methods, the customized MATLAB programs 1) identified the EGJ-midline by searching for minimal diameter values below an investigator-designated (based on review of the FLIP topography plot) proximal border of the EGJ and reconfiguring the data array from this landmark to include an 8-cm measurement segment spanning from three to ten cm above the EGJ and 2) applied a median filter to luminal diameter and intra-balloon pressure data to minimize vascular and respiratory artifact. To derive a pressure value from between-contraction recording segments (i.e. to best reflect the *relaxed* state of the esophageal body), the nadir pressure that occurred during each 5-ml incremental distension volume was selected (Figure 1, bottom panels).

For the WD-method, to identify the narrowest luminal diameter within the esophageal body, a wavelet decomposition (WD) technique was applied to the reconfigured esophageal diameter data to remove the esophageal contraction interference and calculate the median value of the narrowest post-WD diameters during each distension volume (Figure 2). These narrowest-esophageal diameters were plotted by the intra-balloon pressure identified for each 5-ml incremental distension volume (Figure 3).

For the MD-method, the maximal diameters achieved at each impedance planimetry channel during each distension volume were identified; the narrowest of these maximally-achieved diameters for each distension volume, were then plotted by the nadir intra-balloon pressure at each distension volume (Figure 3). We chose to identify the maximally-achieved diameter at each impedance planimetry channel to represent the resting-state (i.e. in-between esophageal contractions) of the esophageal body. This assumed that the limiting degree of luminal distension would be relatively fixed in areas of fibrostenosis and would be identified by selecting the narrowest of these maximal diameters for each distension volume.

The esophageal body diameter-pressure relationship was then modeled with a polynomial regression technique to derive both the WD-DP and the MD-DP (Figure 3).

Additionally, the MATLAB program transformed the esophageal body FLIP data to create a maximal diameter spatial variation plot for the intra-balloon pressure of 40 mmHg (Figure

4); 40-mmHg of intra-balloon pressure was chosen as this seemed to be a reasonable distensive pressure (slightly greater than typical swallow-associated intra-bolus pressure) when luminal resistance associated with EoE-associated fibrostenosis would be encountered. If a pressure of 40-mmHg was not achieved, then the maximal diameters at each channel over the course of the entire distension study were utilized to generate the spatial variation curves. The narrowest diameter observed within this spatial variation plot was then determined and labeled as the 40mmHg restricting diameter (40RD). Finally, the area-under-the-curve (AUC, mm²) for this spatial-variation plot was determined and utilized to calculate an estimated intra-esophageal luminal volume that occurred at 40-mmHg (40LV, ml) by summing the re-configured frustrum volumes of 8-cm of esophageal lumen.

Finally, a *DP* was generated using the FLIP Analytics software, version 1.0.0.1 (Crospon Inc), as depicted in Figure 5. The step-wise, distension protocol of the FLIP study was viewed with a standard average filter set at 20 seconds. The study was paused when the balloon pressure reached 40-mmHg and the narrowest diameter measurement of the esophageal body was recorded as the DP. If the study did not reach an intra-balloon pressure of 40-mmHg, then the narrowest esophageal body diameter at the maximally-achieved distension volume (during a time when no apparent esophageal contraction was occurring) was recorded as the DP.

Statistical analysis

Group values are reported as median (interquartile range, IQR), unless otherwise specified. Comparison of dichotomous and categorical variables between groups was assessed with the χ^2 test. Non-parametric continuous variables were compared between groups with Mann-Whitney U and intra-subject method comparisons were assessed using the Wilcoxon Signed Ranks test. Statistical significance was considered at a two-tailed p-value < 0.05.

Results

Subjects

During the study period, 50 patients with suspected EoE underwent upper endoscopy with FLIP. 17 of these patients were excluded for lack of esophageal eosinophilia (nine had PPI-responsive esophageal eosinophilia, eight had resolution of esophageal eosinophilia following other therapy); five were excluded due to FLIP evaluation prior to a PPI trial. Screening of FLIP topography was then performed for 28 consecutive patients (16 with RACs, 10 without RACs, 2 excluded for technically-limited FLIP studies) to meet the target inclusion of ten EoE patients with RACs (2 female; mean age 35 years, range 19 – 64 years) and ten EoE patients without RACs (2 female; mean age 40 years, range 31 – 54). Some contractility was still present in 8/10 (80%) patients without RACs. Repetitive, retrograde contractions were present in 40% of patients with RACs and 10% of patients without RACs. Patients with RACs and without RACs had similar clinical characteristics (Table 1).

One control was excluded from analysis due to catheter movement that limited esophageal body distensibility analysis. Thus, nine controls (6 female; ages 20 – 49), seven with RACs and two with contractility, but without RACs, were included for analysis.

Esophageal distensibility

The maximum distension volume achieved during stepwise distension was 55 ml (46 – 60) for all patients and 60 ml in all nine controls. The maximum distension volume was 55 ml (49 – 60) among patients with RACs and 55 ml (44 – 60) among patients without RACs.

Distensibility plateau differed between all patients and controls by WD-method ($p = 0.002$) and MD-method ($p = 0.001$); a statistical trend was detected using the FLIP Analytics-method ($p = 0.055$); Table 2. Distensibility plateau did not differ between patients with and without RACs when calculated by all three methods, p-values 0.853 (WD), 0.315 (MD), and 0.280 (FLIP Analytics). The 40RD and 40LV differed between patients and controls (p-values 0.006 and 0.044, respectively), but not between patients with and without RACs (p-values 0.105 and 0.165).

Distensibility plateaus differed within all subjects (combining controls and patients) when calculated with all three different methods, such that the FLIP Analytics DP was less than the WD-DP ($p < 0.001$), which was less than the MD-DP ($p < 0.001$). The difference across methods was also present among all EoE patients (FLIP analytics < WD-DP, $p < 0.001$ and WD-DP < MD-DP, $p < 0.001$) and among controls (FLIP analytics < WD-DP, $p = 0.008$ and WD-DP < MD-DP, $p = 0.008$). Finally, DPs differed by method within subjects both with RACs (FLIP analytics < WD-DP, $p = 0.007$; WD-DP < MD-DP, $p = 0.005$) and without RACs (FLIP analytics < WD-DP, $p = 0.022$; WD-DP < MD-DP, $p = 0.005$). The degree of intra-subject difference in DP measures, however, was more pronounced among controls and patients with RACs, than in patients without RACs, which can be appreciated by the individual variation across DP-methods by contractility groups illustrated in Figure 6. The 40RD was greater than the FLIP Analytics-DP among all subjects ($p < 0.001$), controls ($p = 0.025$), all patients ($p = 0.001$), patients with RACs ($p = 0.005$), and patients without RACs ($p = 0.022$).

Discussion

The main finding of this study was that quantification of esophageal distensibility using the FLIP differs within subjects among different analytic methods and this difference is significantly exaggerated by esophageal contractility. Additionally, we described updated analytic methods to evaluate esophageal body distensibility among EoE patients that incorporated the 16-cm FLIP, which as opposed to the 8-cm FLIP utilized in previous studies in EoE, allowed for visualization of the EGJ as an anatomic reference point during the FLIP study.

Similar to previous studies, we observed a reduction in esophageal distensibility (among all analytic methods) in EoE patients compared with controls. Although the previous studies utilized the 8-cm FLIP and different methods to calculate DP, fairly similar measures of esophageal distensibility were observed in controls (median DPs of 23.6 and 19.8 mm) and among EoE patients with strictures (median DP 14.8 mm), as our cohort predominantly encompassed those with strictures.(3, 5) Kwiatek et al utilized a complex modeling technique to reflect the narrowest esophageal diameter as a function of intra-balloon pressure.(3) Nicodeme et al employed a wavelet decomposition method, as also utilized in

the present study.(5) In both previous studies, when peristalsis was observed on the real-time FLIP display, portions of the FLIP study were repeated in an attempt to minimize the effects of esophageal contractility. As RACs were frequently observed in our study (> 50% of EoE patients evaluated during the screening phase) and often continued throughout the duration of the distension protocol (as in Figure 1A), simply repeating portions of the study may not be feasible. Additionally, repeating portions of the FLIP study (albeit that involved step-wise distension at 2-ml increments to a maximum distension volume of 40-ml), was reported to add 10-15 minutes to the endoscopic procedure; the distension protocol for the present study was typically completed in less than 5 minutes.(3) However, the larger (16-cm) FLIP device may be more prone to induce distension-mediated contractility, which may limit comparison to studies utilizing an 8-cm FLIP.(3, 5) Further, as we demonstrated that distensibility measures were fairly stable within subjects without RACs, pharmacologic inhibition of contractility during the FLIP study could be considered. However, this would carry the potential for medication-associated adverse events.

This study did not demonstrate clinical differences between patients with and without RACs, although this comparison was beyond the aims of this study and thus was limited by the small sample sizes. While the clinical significance of distension-mediated esophageal contractility remains unclear, we clearly demonstrated that esophageal contractility carries a significant effect on analytic methods to quantify esophageal distensibility. However, the ultimate question regarding FLIP evaluation and analysis (and the primary limitation of the study) relates to evaluating *accuracy*, particularly as FLIP measurement may be utilized in real-time to direct when to perform dilation and possibly guide therapeutic dilation size. However, defining an accurate quantification of the narrowest-esophageal luminal diameter to serve as a reference standard for FLIP measurements is difficult. Endoscopy is the primary method utilized, however, at luminal diameters greater than the scope diameter (> 9-10 mm), objective evaluation of stricture or luminal diameter is limited.(11) While our endoscopic assessment of luminal caliber or stricture diameter (or subsequent decision to perform therapeutic dilation) could be considered to assess FLIP-method accuracy, however, the endoscopist was not blinded to the FLIP and thus was potentially influenced by the real-time FLIP interpretation. Unfortunately, response to dilation (i.e. presence or absence of mucosal disruption) was not uniformly reported and thus could not be generally applied. Further, only a portion of our patients with strictures (6/18, 33%), had a stricture reported within the measurement window assessed with the FLIP. Thus, while the EGJ provides a valuable anatomic reference point, including the EGJ in the FLIP-study with a 16-cm device omits evaluation of the proximal esophagus. Barium esophagram could be considered to aid our accuracy assessment, however, esophagram is not routinely done for our EoE patients and was not available for any of the included patients.

Perhaps the most convincing measure of accuracy may be our concept of normality. Although a statistical difference in distensibility measures between controls and EoE patients was identified across all methods, the objective quantification may be more clinically relevant. A landmark study of symptom-presence related to distal-esophageal ring diameter demonstrated that patients never had dysphagia with a ring diameter > 20 mm.(12) When evaluating our data, it is notable that the FLIP Analytics method, which simply averaged luminal diameters, detected a DP < 17-mm in all seven asymptomatic controls with

RACs, but neither control without RACs (Figure 6A). As controls with RACs have contractions that occur at about 8 seconds intervals, last about 5 seconds, and with diameter changes of about 9-mm, it seems intuitive that simply averaging through these contractions will erroneously reduce a distensibility measurement.(8) Even with the WD-method, which aims to filter the contraction-associated diameters changes, three controls had a DP < 17 mm detected and six of seven with RACs had a WD-DP < 19 mm, suggesting the WD-identified diameter ‘baseline’ may still be lower than the actual rested-state diameter of the esophageal body. Use of the MD-method is supported by observing a DP > 19 mm all 9 controls. Additionally, the 40RD was greater than 19 mm in all nine controls. Thus, future study evaluating clinical associations with distensibility measures will help clarify the ideal FLIP measure(s) of esophageal-body distensibility.

Our selection of patients with active esophageal eosinophilia was intended to create a generally homogeneous EoE population, however EoE remains a heterogeneous disorder. Thus not all patients with EoE may be expected to have an ‘abnormal’ DP. Additionally, our patients evaluated with FLIP at an esophageal referral center may reflect more severe or complicated EoE patients than typically evaluated in a community practice, which may limit the generalizability of our findings. Further, as the DP is derived from the single, luminal limiting diameter the DP alone may not completely characterize the degree of diffuse esophageal fibrosis in some patients, such as those with the conceptual narrow-caliber esophagus. Thus, utilization of a measure akin to the 40LV may be valuable to phenotype EoE patients based on the extent and degree of esophageal fibrostenosis. However, this evaluation is beyond the aims of this study and evaluation using additional FLIP concepts, such as esophageal body compliance, to enhance phenotyping within EoE is a goal for future study.

In conclusion, we demonstrated that distension-mediated esophageal contractility has a significant effect on the analytic methods used to quantify esophageal distensibility. We introduced updated analytic methods that both provides assurance of catheter location by utilizing the 16-cm FLIP and also may improve the handling of esophageal contractility. However, further study remains needed to confirm the clinical utility of the MD-DP, 40RD, and/or 40LV as improvements for modeling the esophageal mechanical properties in EoE. Additionally, incorporation of analysis updates into methods available for real-time use will provide the greatest clinical impact by helping direct real-time clinical decisions (e.g. therapeutic dilation). Ultimately, continued improvement of methods to assess esophageal distensibility using the FLIP has the potential to serve as a valuable aid to clinical management and as an objective outcome measure in clinical research studies.

Acknowledgements

None

Grant support: This work was supported by T32 DK101363 (JEP) and R01 DK079902 (JEP) from the Public Health service.

Abbreviations

40RD	40 mmHg restricting diameter
40LV	40 mmHg luminal volume
AUC	area under the curve
DP	distensibility plateau
EGJ	esophagogastric junction
EoE	eosinophilic esophagitis
EREFS	EoE Endoscopic Reference Score
FLIP	functional lumen imaging probe
IQR	interquartile range
MD	maximal diameter
PPI	proton pump inhibitor
RACs	repetitive, antegrade contractions
WD	wavelet decomposition

References

1. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, American College of G. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). The American journal of gastroenterology. 2013; 108(5):679–92. quiz 93. [PubMed: 23567357]
2. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, Straumann A. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013; 145(6):1230–6. e1–2. [PubMed: 23954315]
3. Kwieciek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology. 2011; 140(1):82–90. [PubMed: 20858491]
4. Lin Z, Kahrilas PJ, Xiao Y, Nicodeme F, Gonsalves N, Hirano I, Pandolfino JE. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. Therapeutic advances in gastroenterology. 2013; 6(2):97–107. [PubMed: 23503784]
5. Nicodeme F, Hirano I, Chen J, Robinson K, Lin Z, Xiao Y, Gonsalves N, Kwasny MJ, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013; 11(9):1101–7. e1. [PubMed: 23591279]
6. Lin Z, Nicodeme F, Boris L, Lin CY, Kahrilas PJ, Pandolfino JE. Regional variation in distal esophagus distensibility assessed using the functional luminal imaging probe (FLIP). Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2013; 25(11):e765–71. [PubMed: 23965159]
7. Carlson DA, Lin Z, Rogers MC, Lin CY, Kahrilas PJ, Pandolfino JE. Utilizing functional lumen imaging probe topography to evaluate esophageal contractility during volumetric distention: a pilot study. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2015; 27(7):981–9. [PubMed: 25898916]

8. Carlson DA, Lin Z, Kahrilas PJ, Sternbach J, Donnan EN, Friesen L, Listernick Z, Mogni B, et al. The Functional Lumen Imaging Probe Detects Esophageal Contractility Not Observed With Manometry in Patients With Achalasia. *Gastroenterology*. 2015; 149(7):1742–51. [PubMed: 26278501]
9. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, Haas NA, Romero Y, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014; 147(6):1255–66. e21. [PubMed: 25160980]
10. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013; 62(4):489–95. [PubMed: 22619364]
11. Gentile N, Katzka D, Ravi K, Trenkner S, Enders F, Killian J, Kryzer L, Talley NJ, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. *Alimentary pharmacology & therapeutics*. 2014; 40(11-12):1333–40. [PubMed: 25287184]
12. Schatzki R. The Lower Esophageal Ring. Long Term Follow-up of Symptomatic and Asymptomatic Rings. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine*. 1963; 90:805–10.

Key points

- Esophageal distensibility assessed with the functional lumen imaging probe (FLIP) may be altered in eosinophilic esophagitis (EoE). This study evaluated novel FLIP analytic methods that addressed measurement limitations, notably esophageal contractility.
- Distensibility was reduced in EoE patients compared with controls using multiple analytic methods. More pronounced intra-subject differences were associated with a greater degree of esophageal contractility. The method that measured distensibility by identifying the narrowest of maximal-achieved luminal diameters appeared to be the most promising.
- Our study demonstrates the importance of recognizing and accounting for contractility during esophageal-body distensibility evaluation with the FLIP.

Figure 1. FLIP Topography plots

Examples of EoE patients with repetitive, antegrade contractions (RACs) (**A**) and without RACs (**B**) are displayed. The topographic plots (top-panels) represent color-coded *diameter*-plots generated from interpolation of the impedance-planimetry data by spatial orientation (y-axis) by time (x-axis). The 8-cm of the topographic plot above the white line, which represents 3-cm above the EGJ midline, was subjected to analysis of esophageal body distensibility. The intra-balloon pressure (blue line) and the volumetric distension protocol (black line) are represented in the bottom panels. The nadir pressures identified at each distension volume (black dots) were utilized to create distensibility plots. Notably, the distension protocol in **A** only extended to 40-ml, likely related to the contraction-associated pressure peaks of > 60-mmHg, while the distension protocol in **B** was able to extend to a 60-ml fill volume.

Figure 2. Wavelet decomposition

Diameter measures after wavelet decomposition (blue lines) are overlaid on the original diameter data (red) for the 8-cm of impedance planimetry data within the esophageal body for the same EoE patients displayed in Figure 1. The greater overall degree of filtering, i.e. change in analyzed diameters, in the patients with repetitive, antegrade contractions (RACs) (A) compared to the patient without RACs (B) can be appreciated.

Figure 3. Distensibility plateau (DP)

The data points represent the corresponding narrowest diameter, identified using the wavelet decomposition (WD)-method (circles), and maximal diameter (MD)-method (squares), and nadir intra-balloon pressures that were identified at each 5-ml step-wise distension volume. The DP was calculated based on the plotted polynomial curve. Examples from the same two EoE patients as Figures 1-2 with (A) and without (B) repetitive, antegrade contractions (RACs), as well as two control subjects (red), one with (A) and one without RACs (B), are displayed. The difference between methods among subjects with RACs (A) can be appreciated, while in those subjects without RACs (B), the WD and MD-DP plots are nearly super-imposed.

Figure 4. The 40-mmHg restricting diameter (RD) and luminal volume (LV)

Examples from the same two EoE patients and same two controls (red) as Figure 3 with (A) and without (B) repetitive, antegrade contractions (RACs) are displayed. The narrowest diameter along the spatial variation plot (purple circles) were identified as the RD. The area-under-the-curve (purple for the EoE patients) was transformed to generate the 40LV.

Figure 5. Flip Analytics – distensibility plateau (DP)

Examples from the same two EoE patients with (A) and without (B) RACs are displayed; DPs were 11.4 mm (evaluation of the top channel was omitted) (A) and 10.3 mm (B).

Figure 6. Intra-subject comparison of distensibility plateau analytic methods

Distensibility plateau measures from each subject (**A.** Controls, **B.** EoE patients with repetitive, antegrade contractions (RACs), and **C.** EoE patients without RACs) are represented across analysis methods. A lesser degree of intra-subject variation was observed among subjects without RACs, which are represented with white squares; circles indicate subjects with RACs.

Table 1
Clinical characteristics among EoE patients by contractility status

Values are median (IQR) unless otherwise stated.

	All patients	With RACs	Without RACs	p-value ^I
Symptom score	35 (29 – 47)	30 (15 – 41)	40 (33 – 45)	0.315
Treatment				
PPI/H2RA (%)	80/5	70/10	90/0	0.453
Steroid (%)	15	10	30	0.582
Diet (%)	15	30	0	0.211
Endoscopic (EREFS)				
Edema	1 (0 – 1)	0.5 (0 – 1)	1 (0 – 1)	0.481
Rings	2 (1 – 2)	2 (1 – 2)	2 (1 – 3)	0.631
Exudate	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0.579
Furrows	1 (1 – 1)	1 (1 – 1)	1 (0.5 – 1)	0.968
Stricture (% present)	95	90	90	1.0
Estimated stricture diameter (mm)	12.5 (10 – 15)	13 (12 – 15)	10 (9 – 14)	0.136
Therapeutic dilation performed (%)	60	60	60	1.0
Eosinophil count (per hpf)	40 (25 – 79)	70 (24 – 92)	39 (23 – 53)	0.353

^IComparison of patients with and without RACs. H2RA – histamine 2 receptor antagonist

Table 2

Comparison of esophageal body distensibility measures

Measure	Controls	All patients	With RACs	Without RACs
<i>Wavelet decomposition (WD)</i>				
WD – DP (mm)	18.2 (16.6 – 20.2)	<u>14.5 (11.8 – 16.4)^I</u>	<u>14.8 (12.0 – 16.2)</u>	<u>14.0 (11.6 – 17.8)</u>
<i>Maximal diameter (MD)</i>				
MD-DP (mm)	21.0 (20.3 – 21.6)	<u>16.6 (13.8 – 19.3)^I</u>	<u>17.6 (15.1 – 19.6)</u>	<u>15.6 (12.1 – 18.0)</u>
40RD (mm)	20.9 (19.2 – 21.4)	<u>16.5 (13.6 – 19.1)^I</u>	<u>17.5 (16.0 – 19.8)</u>	<u>13.9 (11.6 – 17.5)</u>
40LV (ml)	28.7 (25.6 – 38.1)	<u>22.8 (17.8 – 28.5)^I</u>	<u>25.8 (20.3 – 36.4)</u>	<u>19.2 (12.5 – 27.0)</u>
Flip Analytics – DP (mm)	15.4 (13.2 – 18.2)	<u>12.9 (10.6 – 15.2)^I</u>	12.4 (10.1 – 14.4)	12.7 (10.2 – 17.0)

^IP-value < 0.05 compared with controls.

There were no statistical differences between patients with and without RACs. WD – wavelet decomposition. MD – maximal diameter. DP – distensibility plateau. RD – restricting diameter. LV – luminal volume.