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ORIGINAL ARTICLE

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Relaxation of the lower esophageal sphincter in response to reduced volume distension during FLIP Panometry

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Abstract

Background: The esophageal response to stepwise distension during the functional lumen imaging probe (FLIP) Panometry study often parallels high-resolution manometry (HRM) motility diagnoses. This study aimed to describe the changes in FLIP metrics during FLIP emptying, that is, reduced volume distension.

Methods: Adult patients who completed FLIP and HRM for esophageal motility evaluation were included. Esophagogastric junction (EGJ) opening parameters were assessed during stepwise FLIP filling to volumes of 60 mL ("filling 60 mL"), then 70 mL, and then back to 60 mL ("emptying 60 mL"). HRM studies were analyzed per Chicago classification version 4.0 (CCv4.0).

Key Results: Among 265 patients included, HRM/CCv4.0 diagnoses included achalasia in 80 patients (30%), normal motility in 70 (26%), and ineffective esophageal motility (IEM) in 43 (16%). EGJ-distensibility index (DI) and EGJ diameter were greater during emptying 60 mL than filling 60 mL in achalasia, normal motility, and IEM (p values <0.002). If applying the emptying 60 mL EGJ-DI (vs. filling 60 mL EGJ-DI), EGJ opening classification changed from reduced EGJ opening to borderline EGJ opening in 31% of achalasia patients and in 2% of patients with normal motility or IEM. EGJ opening classification was unchanged in 69% achalasia and 96% of normal motility/IEM.

Conclusions and Inferences: This study suggests that isotonic or auxotonic relaxation of the lower esophageal sphincter occurs with reduced volume distension in patients with achalasia and normal motility. The study also supports the importance of utilizing a standardized FLIP motility study protocol (i.e., controlled, stepwise filling to 50 mL, 60 mL, then 70 mL) to provide reliable and generalizable FLIP metrics to facilitate diagnosis of esophageal motility disorders.

KEYWORDS
achalasia, esophageal motility disorders, impedance, manometry

Abbreviations: BMI, body mass index; CSA, cross-sectional area; DI, distensibility index; EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; IRP, integrated relaxation pressure; IQR, interquartile range; LES, lower esophageal sphincter.

1 | INTRODUCTION

Functional lumen imaging probe (FLIP) Panometry uses high-resolution impedance planimetry technology during volume-controlled distension to assess the mechanical properties of the esophageal wall and the esophagogastric junction (EGJ). It analyzes lumen dimensions by determining multiple adjacent cross-sectional areas (CSA) and the CSA-pressure relationship (distensibility) of the distended area by measuring the intrabag pressure.[1–3]

Physiologic bolus transport through the EGJ requires synchronized muscle movements with relaxation and opening of the lower esophageal sphincter (LES) immediately before and during passage of the food bolus in response to pressure. It also depends on the biomechanical properties of the esophagus in terms of pressure-geometric data which cannot be fully assessed using high-resolution manometry (HRM).[4] EGJ opening dynamics are complex and rely on an interplay between multiple factors including the LES, the crural diaphragm (and their relative locations, e.g., hiatal hernia), as well as esophageal peristalsis. Through assessing the EGJ as a three-dimensional structure[5,6] by providing a direct dynamic measurement of EGJ diameter and distensibility in response to volume distention, along with the esophageal secondary peristalsis, FLIP Panometry allows for the classification of esophageal motility and EGJ opening.[2,4] Thus while FLIP Panometry can assess related esophageal motor characteristics as HRM, it also provides the ability to measure wall stiffness and luminal narrowing in various esophageal diseases.[5]

Although FLIP is uniquely suited to characterize EGJ function at the time of sedated endoscopy for clinical diagnosis and therapeutic follow-up of esophageal motility disorders,[7] the mechanisms related to the esophageal response to FLIP distension remain incompletely understood. In particular, abnormal EGJ distensibility can be observed among patients with normal motility (i.e., normal LES relaxation pressure and normal primary peristalsis) on HRM.[8,9] While this finding was sometimes associated with increased esophageal retention on esophagram, as well as a FLIP response including sustained LES contraction (a potentially spastic motor response), it also carries the potential for clinical uncertainty and thus was of interest for further investigation. Given the difference in esophageal function tested with HRM (i.e., response to swallows) versus FLIP (response to sustained distension), we hypothesized abnormal EGJ response may be linked to an abnormal LES contraction in response to distension. Hence, we hypothesized that emptying of the bag that reduces the distensive stimuli would potentially allow EGJ distensibility to normalize if inhibitory LES function is intact.

Therefore, the aim of this study was to describe the effects of reduced volume distension (i.e., emptying of the FLIP bag) on the EGJ FLIP metrics (EGJ diameter, FLIP pressure, and EGJ-distensibility index [DI]) across the spectrum of motility disorders as defined by HRM using the Chicago Classification version 4.0 (CCv4.0). Further, the impact and clinical significance of this FLIP response on reclassifying EGJ opening on FLIP was described with a focus among patients with normal deglutitive EGJ pressures on HRM (i.e., normal motility and ineffective esophageal motility).

Key points

- The esophageal response to sustained distension is evaluated during functional lumen imaging probe (FLIP) Panometry; this study aimed to study the changes in FLIP metrics during emptying of the FLIP, i.e. reduced volume distension.
- On comparison with the standard FLIP filling protocol (60ml), FLIP metrics after partial emptying showed an increase in EGJ-distensibility index and increase in EGJ diameter where as FLIP pressure and contractile response pattern were similar. These findings were observed in both achalasia and patients with normal esophageal motility.
- The study results support the importance of utilizing a standardized FLIP motility study protocol (i.e., controlled, stepwise filling to 50ml, 60ml, then 70ml) to provide reliable and generalizable FLIP metrics to facilitate diagnosis of esophageal motility disorders.

2 | METHODS

2.1 | Subjects

Consecutive adult patients (ages 18–89 years old) presenting to the Esophageal Center of Northwestern for evaluation of primary esophageal motility disorders between January 2020 and November 2021, who completed HRM and FLIP during upper endoscopy were included. There was no endoscopic or surgical treatment between FLIP or HRM. Patients with technically limited FLIP or HRM studies were excluded as were patients with previous foregut surgery, pneumatic dilation, esophageal mechanical obstruction including stricture, malignancy, eosinophilic esophagitis, severe reflux esophagitis (Los Angeles classification C or D), and hiatal hernia >3 cm as these are potential causes of secondary esophageal motor abnormalities. Additional clinical evaluation with timed barium esophagram (TBE) was obtained at the discretion of the primary treating gastroenterologist. The study protocol was approved by the Northwestern University Institutional Review Board.

2.2 | FLIP study protocol

The FLIP study using 16-cm FLIP (EndoFLIP® EF-322 N; Medtronic, Inc, Shoreview, MN) was performed in the left-lateral decubitus position during endoscopy using sedation with midazolam (0–15 mg) and fentanyl (0–250 mcg); propofol was used with anesthesiologist assistance at the discretion of the performing endoscopist in some cases. Although these medications used for endoscopic sedation can alter esophageal motility, the patterns of motility during the

FLIP protocol are reproducible and predictable during standard manometry performed without these medications.[3,10–12] With the endoscope withdrawn and after calibration to atmospheric pressure, the FLIP was placed transorally and positioned within the esophagus with 1–3 impedance sensors beyond the EGJ with this positioning maintained throughout the study. Stepwise 10-ml FLIP distensions beginning with 40 mL and increasing to target volume of 70 mL were then performed; each stepwise distension volume was maintained for 60 s. While maintaining positioning, the FLIP was then emptied to 60 mL for another 60 s (Figure 1).

2.3 | FLIP Panometry analysis

FLIP data were exported to a customized program (available open source at http://www.wklytics.com/nmgi) to generate FLIP Panometry plots for analysis to assess the esophageal contractile response to distension and to classify EGJ opening.[9] FLIP Panometry analysis was performed blinded to clinical data including HRM results and treatment plan. The analysis of EGJ opening applied the EGJ-DI (with associated EGJ diameter and FLIP pressure) at the filling and emptying 60 mL-fill volume. The maximum EGJ diameter was measured during the filling 60 mL or 70 mL-fill volume.[8] Areas at the EGJ that were affected by dry catheter artifact (i.e., artifact that impacts diameter measurement when occlusion of the FLIP bag disrupts the electrical current utilized for the impedance planimetry technology) and the first 5 s after achieving the 60 mL and 70 mL-fill volume (to avoid incorporation of active filling effects) were omitted from the EGJ analysis.[8] The EGJ-DI, EGJ diameter, and FLIP pressure were measured at the peaks of EGJ opening (greatest diameters) during filling and emptying at the 60 mL-fill volume; the median of the three values was then applied for analysis. The EGJ-DI was not calculated if the applied FLIP pressure was <15 mmHg; in these cases (two patients from this cohort), the other EGJ metrics were applied for analysis. EGJ opening was then classified as reduced EGJ opening (REO), borderline-reduced EGJ opening (BrEO), borderline-normal EGJ opening (BnEO), or normal EGJ opening (NEO).[8] The filling EGJ opening classification applied the filling 60 mL EGJ-DI and maximum EGJ diameter from the filling 60 mL or 70 mL-fill volume. The emptying EGJ classification applied the emptying 60 mL EGJ-DI and the maximum EGJ diameter from the 60 mL or 70 mL-fill volume. The EGJ opening classification and the FLIP Panometry contractile response patterns are described in Table S1.

2.4 | HRM protocol and analysis

After a minimum 6-h fast, HRM studies were completed using a 4.2 mm outer diameter solid-state assembly with 36 circumferential pressure sensors at 1 cm intervals and 18 impedance segments at 2 cm intervals (Medtronic Inc, Shoreview, MN). The HRM assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with approximately three intragastric pressure sensors. After a 30-s baseline recording (during which the basal EGJ pressure was measured during end-expiration), the HRM protocol was performed with ten, 5 mL liquid swallows in a supine position and with five, 5 mL liquid swallows in an upright, seated position. HRM studies were analyzed and interpreted according to the CCv4.0, blinded to clinical data including FLIP results and treatment plan.[13,14] HRM/CCv4 diagnoses are reported relative to manometric impression alone (i.e., FLIP, TBE, or symptoms were not applied to clarify monometrically inconclusive results).

2.5 | TBE protocol and analysis

During timed barium esophagram, patients were in the upright position and consumed 200 mL of low-density barium sulfate with images obtained at 1 and 5 min.[15–17] The height of the barium column was measured vertically from the EGJ. In some cases, especially when there was no barium retention, a 12.5 mm barium tablet was also administered, and images obtained at timed intervals until passed into the stomach. TBE was considered normal if there was no barium column or if it was less than 5 cm at 1 min[16] and if there was no retention at 5 min and/or if the tablet passed into the stomach. That is, a TBE with 1 min column height >5 cm, any column presence at 5 min, or impaction of the12.5 mm barium tablet was considered abnormal. Presence of an epiphrenic diverticula was also included among abnormal esophagram.[16,17]

2.6 | Symptom scores

Many subjects completed validated self-reported symptom scores at the time of testing with FLIP and HRM including, Brief Esophageal Dysphagia Questionnaire (BEDQ)[18] and GerdQ.[19] Because some patients chose not to complete the symptom questionnaires, these were not available for all subjects. The BEDQ included eight 6-point Likert scale questions (scored 0–5)

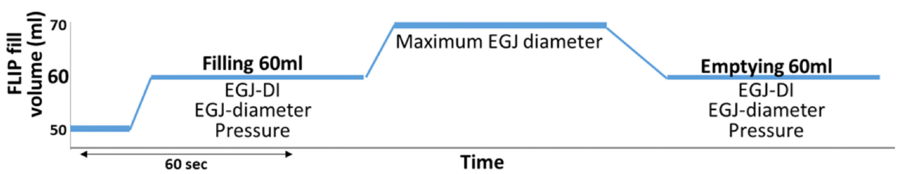

FIGURE 1 FLIP study protocol to assess response to reduced volume distension. EGJ, esophagogastric junction; DI, distensibility index.

that assessed the frequency and severity of dysphagia over the preceding 14-days; items were summed to yield scores ranging from 0 (asymptomatic) to 40, with greater scores indicating greater dysphagia severity. The GerdQ is a 6-item self-report measure used to support gastroesophageal reflux disease's (GERD) diagnosis. The items assess the frequency of symptoms and medication use over the preceding 7 days and the GerdQ score is generated by summing four graded Likert scale items of four positive predictors (scored 0–3) and two reverse Likert scale items of negative predictors (scored 3–0).

2.7 | Statistical analysis

Results were reported as mean (standard deviation; SD), or median (interquartile range; IQR) depending on data distribution. Groups were compared using ANOVA (two-way ANOVA, two-way mixed ANOVA), independent *t*-tests, or Kruskal–Wallis test for continuous variables, depending on data distribution as well as chi-square test of independence, Fischer's exact test, and Mc Nemar's test for categorical paired variables. For intra (within)-subjects' comparisons, Wilcoxon signed-rank test and paired samples *t*-tests were utilized. Statistical significance was considered at a 2-tailed p value <0.05. Post hoc comparison testing, when appropriate, was completed using a Bonferroni correction.

3 | RESULTS

3.1 | Subjects

A total of 265 patients (18–85 years), mean age 53.4 years (SD 16.4), 64% female, were included; Table 1; Figure S1. Dysphagia was the most common indication for evaluation representing 80% of the cohort. The most common HRM motility diagnoses were achalasia in 80 patients (30% of the cohort) and normal motility in 70 patients (26%). Due to the rarity of the hypercontractile esophagus (HC) and the distal esophageal spasm (DES), the two were combined into one category "DES-HC" for analysis.

TABLE 1 Cohort characteristics.

	All patients	Subgroup Normal/IEM
N (frequency)	265	113
Age, mean (SD), year	53.4 (16.4)	50.6 (16.3)
Sex, female, *n* (%)	169 (64)	31 (27)
BMI, mean (SD) kg/m^2	27.5 (6.7)	26.5 (5.7)
Indication, *n* (%)		
Dysphagia	211 (80)	85 (75
Reflux symptoms	19 (7)	15 (13)
Chest pain	10 (4)	5 (4)
Other (follow-up, preoperative)	25 (9)	8 (7)
Endoscopy findings, *n* (%)		
Erosive esophagitis: LA-A/B	9 (3)	7 (6)
Nonobstructing ring	7 (3)	4 (4)
Diverticulum	9 (3)	4 (4)
HRM-EGJ morphology, *n* (%)		
Type I (no hiatal hernia)	149 (56)	31 (27)
Type II-III (hiatal hernia)	116 (44)	82 (73)
Timed barium esophagram (TBE)		
Normal	52 (20)	38 (34)
Abnormal[a]	70 (26)	9 (8)
No TBE/missing	143 (54)	66 (58)
BEDQ score, mean (SD)	12.4 (10.4)	9.5 (9.3)
Not completed, *n* (%)	42 (16)	9 (8)
GerdQ score, mean (SD)	8.8 (2.9)	8.3 (2.8)
Not completed, *n* (%)	34 (13)	6 (5)
HRM-Chicago Classification v4.0, *n* (%)		
Type I achalasia	29 (11)	–
Type II achalasia	35 (13)	–
Type III achalasia	16 (6)	–
EGJ outflow obstruction	51 (19)	–
Normal motility	70 (26)	70 (62)
Ineffective esophageal motility	43 (16)	43 (38)
Absent contractility	15 (6)	–
Hypercontractile esophagus	4 (2)	–
Distal esophageal spasm	2 (1)	–

[a]abnormal TBE is defined as a 5-minute column height >5 cm or a 1-minute column height >5 cm in addition to impaction of the 12.5-mm barium tablet in the stomach.

3.2 | Comparison of FLIP metrics between FLIP filling and emptying

There were differences between CCv4.0 diagnoses during both filling and emptying in EGJ-DI (p values <0.001), EGJ diameter (p values <0.001), and pressure (p values <0.001); Figure 2. In particular, EGJ-DI and EGJ diameter (both during filling and emptying) were lower in achalasia than in normal motility, IEM, and absent contractility (adjusted p values <0.001). FLIP pressure was lower in achalasia and absent contractility than in normal motility and EGJOO during both filling and emptying (adjusted p values <0.006). The median (5–95th percentiles) of EGJ-DI in achalasia patients (including subtypes I, II, and III) was 1.3 mm^2/mmHg (0.4–3.1) during filling and 2.2 mm^2/mmHg (0.8–4.6) during emptying.

The maximum EGJ diameter also differed between HRM motility diagnoses (p=0.001) and was lower in achalasia than in EGJOO, absent contractility, IEM, and normal motility (adjusted p values <0.05); Figure 2. Emptying EGJ diameter was greater than the maximum EGJ diameter (i.e., from filling 60 or 70 mL-fill volumes) in 44 patients (17%

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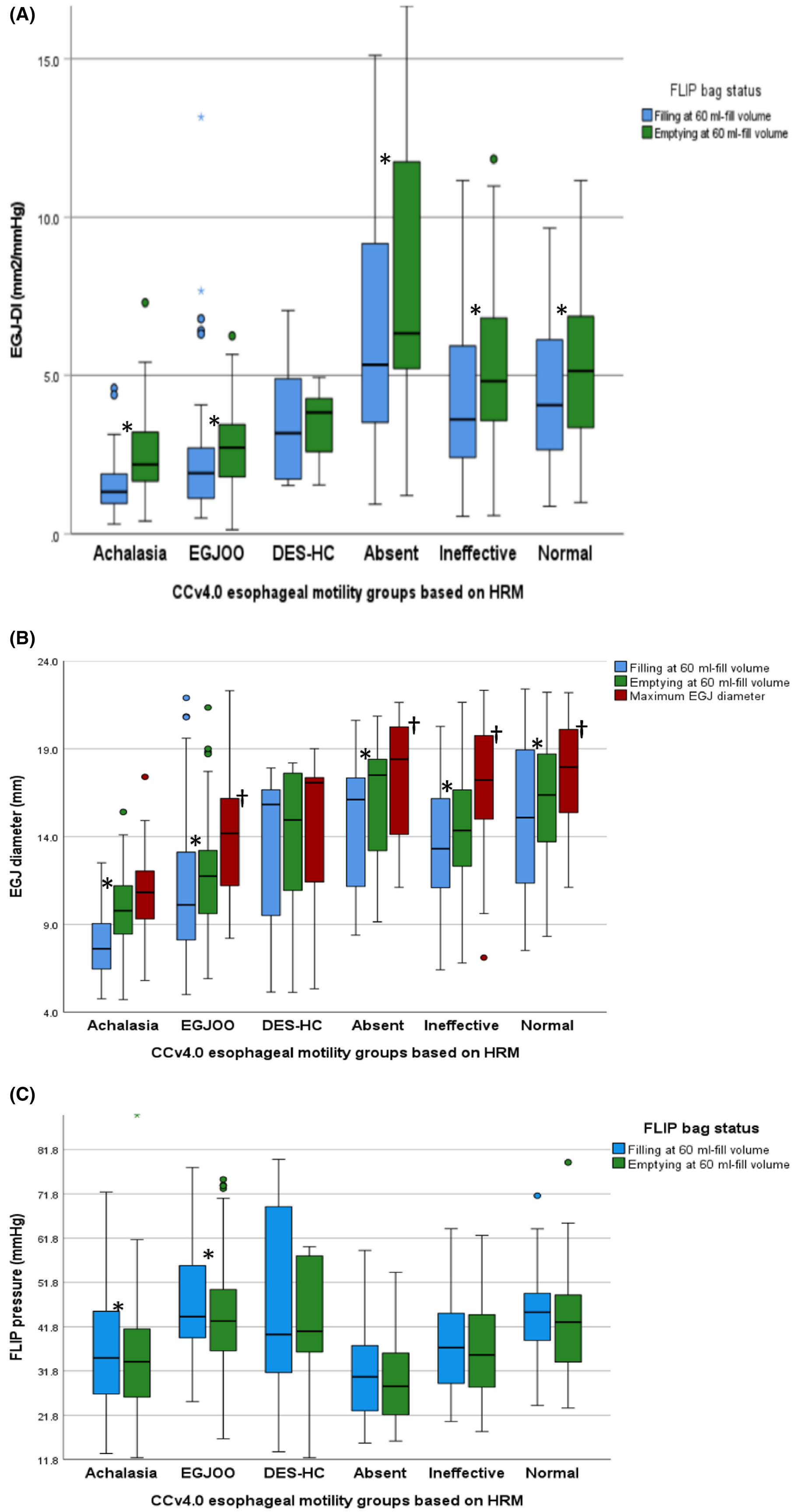

FIGURE 2 Comparison of filling and emptying FLIP metrics among HRM-motility diagnosis. (A) EGJ-DI, (B) EGJ diameter and maximum EGJ diameter, and (C) FLIP pressure on filling (blue) and emptying (green) of the FLIP (60-ml fill volume) across the esophageal motility groups defined by HRM. "*" indicate a statistically significant difference ($p < 0.05$) on within-subjects' comparisons (emptying versus filling). "†" indicate a statistically significant difference ($p < 0.05$) on between groups' comparisons with achalasia. a Maximum EGJ diameter was measured during the filling 60 ml or 70 ml-fill volume (highest value). EGJOO, EGJ outflow obstruction; DES, distal esophageal spasm; HC, hypercontractile; IEM, ineffective. esophageal motility.

of the entire cohort), though greater by more than 1 mm in 18 patients (7% of entire cohort); frequency of either increase did not differ between HRM diagnosis (*p* values 0.19 and 0.527, respectively).

On paired, intrasubject comparison between filling and emptying metrics, the EGJ-DI and EGJ diameter were greater during emptying within all CCv4.0 motility diagnoses (*p* values ≤0.002), except for among the DES-HC; Figure 2. The absolute changes (i.e., emptying minus filling) among the entire cohort were median (IQR) 0.9 (0.3–1.5) mm^2/mmHg for EGJ-DI, 1.5 (0.3–2.7) mm for EGJ diameter. There was not a statistically significant difference in absolute change in EGJ-DI between HRM motility diagnoses ($p=0.212$), but there was a statistically significant difference in absolute change in EGJ diameter ($p=0.002$), with achalasia having a *greater* increase in EGJ diameter than in normal motility ($p=0.009$). There was not a difference in absolute change in EGJ diameter between achalasia subtypes ($p=0.618$).

While the FLIP pressure was significantly lower during emptying than filling in achalasia, EGJOO, and absent contractility, the absolute change in FLIP pressure (i.e., emptying minus filling) among these groups were median (IQR), −2.1 mmHg (−4.9 to −0.3), −2.4 mmHg (−7.7 to 1.3), and − 0.4 mmHg (−4.0 to 0.5) mmHg, respectively; Figure 2. There was not a significant difference in FLIP pressure between filling and emptying within the other HRM diagnoses. For the entire cohort, the absolute change in FLIP pressure was −1.8 (−5.0 to 1.3) mmHg; Figure 3.

Regarding contractile response, there were antegrade contractions present during both the filling 60 mL and emptying 60 mL in 61 (23% cohort) and no antegrade contractions during both filling and emptying 60 mL in 188 patients (71% cohort), thus unchanged in 94% of the cohort. There were 12 (5%) patients with antegrade contractions during filling 60 mL but not emptying 60 mL, and in 4 (1%) patients there were antegrade contractions during emptying but not during filling 60 mL. EGJ-DI was greater during emptying 60 mL than filling 60 mL in patients with no change in contractile response (Table 2), but there were not significant differences between filling 60 mL and emptying 60 mL EGJ-DI in patients with a change in contractile response. However, 6/12 (50%) of patients with antegrade contractions during filling 60 mL that did not have antegrade contractions during emptying 60 mL had a *decrease* in EGJ-DI >1.0 mm^2/mmHg from filling to emptying. A decrease in EGJ-DI >1.0 mm^2/mmHg from filling to emptying occurred in only 3% from the remainder of the cohort (9/253 patients).

3.3 | Impact of emptying EGJ-DI on EGJ opening classification

In achalasia patients (including subtypes I, II, and III), during filling 60 mL, 81% of patients had EGJ-DI <2.0 mm^2/mmHg, while with emptying 60 mL, EGJ-DI was <2.0 mm^2/mmHg in 44%; Figure 4. The EGJ opening classification applying the 60 mL filling EGJ-DI was REO in 68%, BrEO in 26%, BnEO in 6%, and NEO in 0 patients; Figure 5. If applying the emptying EGJ-DI to EGJ opening classification, 40% had REO, 54% BrEO, 5% BnEO, and 1% ($n=1$) had NEO. Thus, EGJ opening classification changed in 31% of achalasia patients. Only one patient changed from BEO to NEO (who had type III achalasia on HRM and a 5-min column height of 12 cm on TBE) and one from BEO to REO; the remainder (23/25; 92%) were from REO to BEO; Figure 5.

In patients with normal motility or IEM on HRM, during filling 60 mL, 12% ($n=13$) had an EGJ-DI <2.0 mm^2/mmHg while with emptying, EGJ-DI was <2.0 mm^2/mmHg in 6% ($n=7$); Figure 4. However, among those with filling EGJ-DI <2.0 mm^2/mmHg, none had an emptying EGJ-DI that exceeded the 95th percentile of emptying EGJ-DI in achalasia (4.6 mm^2/mmHg); Figure 4. In patients with normal motility or IEM on HRM, the EGJ opening classification applying the filling EGJ-DI was REO in 4% ($n=4$), BrEO in 12% ($n=14$), BnEO in 15% ($n=17$), and NEO in 69% ($n=78$) of patients; Figure 5. If applying the emptying EGJ-DI to EGJ opening classification, 2% ($n=2$) had REO, 12% ($n=14$) BrEO, 17% ($n=19$) BnEO, and 69% ($n=78$) had NEO. Thus, EGJ opening classification changed in 4% ($n=4$ patients): two from REO to BrEO and two from BrEO to BnEO. Zero patients changed from REO or BEO to NEO.

Finally, clinical characteristics were compared between patients with normal motility or IEM based on change in EGJ opening classification between filling and emptying. Only four normal motility/IEM patients had a change in EGJ opening classification (each patient described in Table S2): all were evaluated for dysphagia and three of the four patients had a spastic-reactive contractile response pattern.

Additionally, changes in EGJ-DI relative to a 2.0 mm^2/mmHg threshold were also assessed among patients with normal motility or IEM on HRM; Table 3; Figure 4. While there were not differences between patients with "normalization" in EGJ-DI (i.e., <2.0 mm^2/mmHg on filling to ≥2.0 mm^2/mmHg on emptying) compared with patients with consistently normal EGJ-DI (≥2.0 mm^2/mmHg during filling and emptying) in BMI, symptoms scores, rates of hiatal hernia, or endoscopy and TBE findings, they did differ with regard to contractile response pattern ($p=0.043$). Contractile response patterns with distinct antegrade contractions (i.e., normal and borderline contractile response) was more frequent in the consistently normal EGJ-DI group (54%; 52/97 patients) versus only 11% (1/9 patients) in the "normalization" of EGJ-DI subgroup.

4 | DISCUSSION

This study that included 265 patients evaluated using FLIP during sedated endoscopy and HRM was the first to describe the impact of reduced volume distension (i.e., emptying of the FLIP bag) on FLIP metrics of EGJ distensibility relative to CCv4.0 motility diagnoses. The key findings were that EGJ-DI was generally greater during the emptying phase (than the filling) of the FLIP protocol among patients both with and without normal deglutitive LES relaxation (i.e., normal IRP) on HRM. Further, the change in EGJ-DI was typically related to an increase in EGJ diameter, with small to no change in FLIP pressure. Finally, although we hypothesized that including an emptying portion in the FLIP protocol could be useful among patients with normal LES relaxation on HRM, but abnormal EGJ opening on FLIP, we instead found that changes in EGJ opening classification were infrequent among this group and not consistently associated with relevant clinical markers to guide its use for this application. Overall, the findings of this study support the importance of utilizing a standardized FLIP study protocol to provide reliable and generalizable application of FLIP metrics to clinical diagnoses. It also offers insights

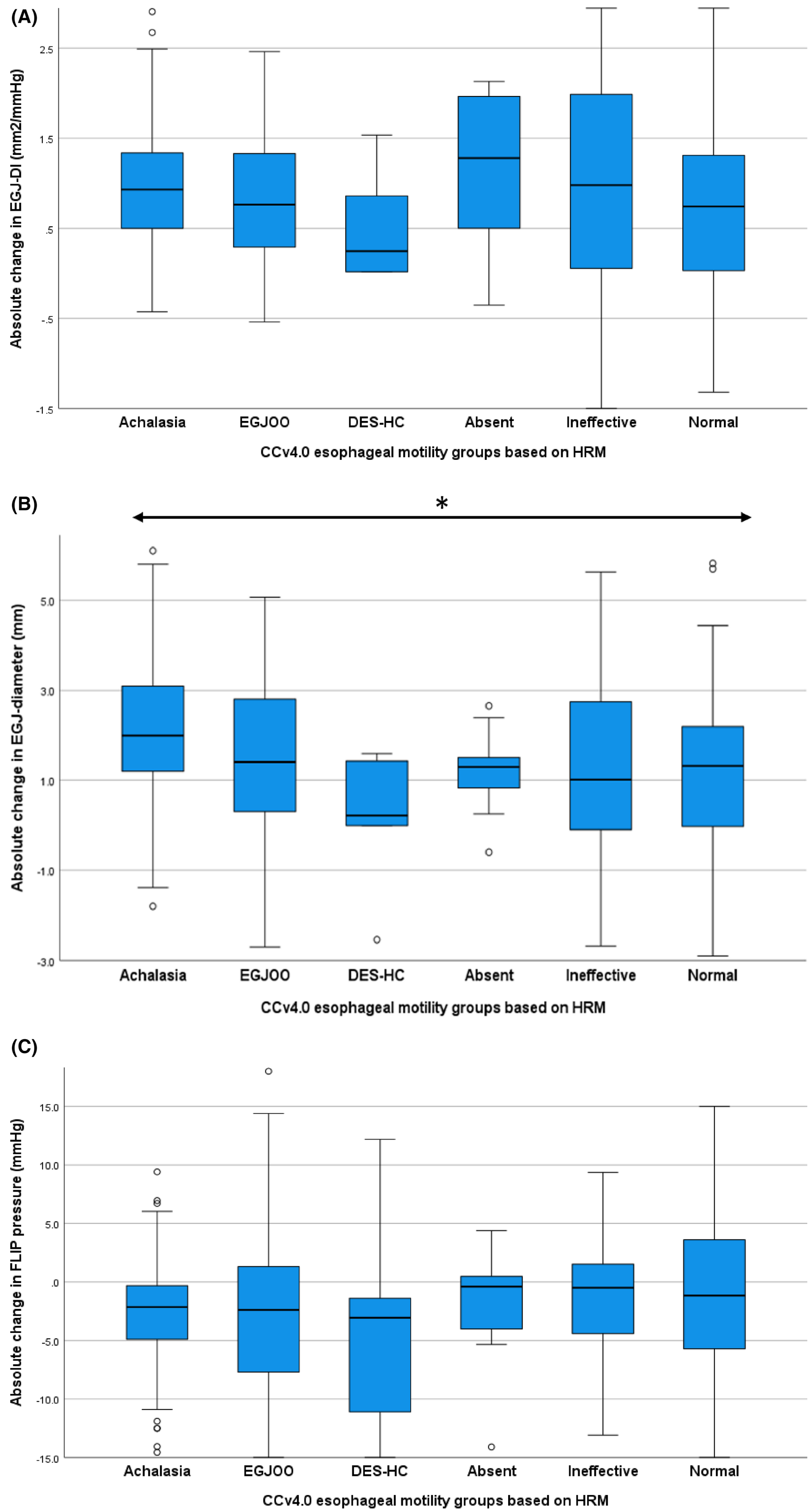

FIGURE 3 Comparison of absolute changes (i.e., emptying minus filling) in FLIP metrics between HRMmotility diagnosis: (A) EGJ-distensibility index (DI), (B) EGJ-diameter, and (C) FLIP pressure. "*" indicates adjusted p-value <0.05. EGJOO, EGJ outflow obstruction. DES, distal esophageal spasm; HC, hypercontractile; IEM, ineffective esophageal motility.

into the physiology of the esophageal response to distension that is observed with FLIP.

Evaluation of EGJ distensibility and opening with FLIP offers a useful addition in the evaluation of esophageal motility disorders. Multiple studies have demonstrated that EGJ distensibility is reduced in achalasia.[20–23] Additionally, several studies have demonstrated that evaluating EGJ distensibility/opening among patients with inconclusive achalasia or manometric EGJOO

TABLE 2 Changes in EGJ-distensibility between FLIP filling and emptying relative to contractile response.

Contractile response status (filling vs. emptying 60 mL)	No change	No change	Change	Change
Filling 60 mL Antegrade contractions	Present	Absent	Present	Absent
Emptying 60 mL: Antegrade contractions	Present	Absent	Absent	Present
n (%)	61 (23)	188 (71)	12 (5)	4 (1)
Filling 60 mL EGJ-DI, mm²/mmHg	5.1 (4.0–7.0)	1.8 (1.1–2.9)	4.0 (3.2–5.6)	2.0 (1.9–2.1)
Emptying 60 mL EGJ-DI, mm²/mmHg	5.6 (4.2–7.4)*	3.0 (1.8–4.3)*	4.0 (1.8–6.5)	4.1 (4.0–4.3)
Filling 60 mL EGJ diameter, mm	18.4 (14.6–19.9)	9.4 (7.3–11.7)	15.3 (12.7–17.6)	9.6 (8.3–11)
Emptying 60 mL EGJ diameter, mm	18 (15.7–20)	11.4 (9.5–13.7)*	15.4 (10.1–17.1)	12.8 (11.3–15.3)
Filling 60 mL FLIP pressure, mmHg	46 (40–55)	37 (29–46)	46 (40–53)	36 (27–52)
Emptying 60 mL FLIP pressure, mmHg	44 (37–52)*	36 (27–45)*	41 (32–49)*	33 (26–43)

Note: Values reflect median (interquartile range) unless otherwise stated.

Abbreviation: DI, distensibility index.

*$p < 0.05$ on intrasubject comparison of corresponding metric at filling 60 mL.

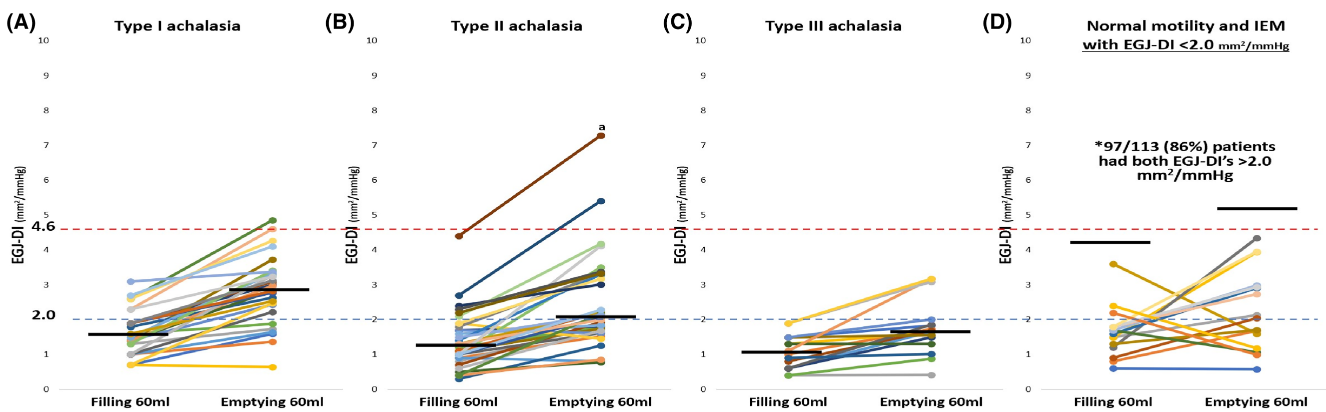

FIGURE 4 Change in EGJ-distensibility index (DI) during FLIP filling compared to FLIP emptying. Horizontal black bars indicated median values. *The median bar represents the entire subgroup of normal motility/ineffective esophageal motility (IEM), though the 97 normal/IEM manometry patients with both filling and emptying EGJ-DI >2.0 mm2/mmHg (85.8% of the subgroup) are not displayed for illustrative purposes. An EGJ-DI of 4.6 mm2/mmHg (red dashed line) was the 95th percentile of all achalasia patients in this cohort. [a]Achalasia outlier with normal range EGJ-DIs related to FLIP pressure (21 mmHg at filling 60 ml; 18 mmHg at emptying 60 ml). The maximum EGJ diameter (60 ml or 70 ml) was 13.3 mm, thus classified as "borderline reduced EGJ opening".

can help identify patients with a "conclusive" disorder of EGJ outflow, thus utilization of FLIP in this scenario was recommended by the CCv4.0.[13,24–26] Further, FLIP metrics of EGJ-DI and maximum EGJ diameter, as well as an associated classification of EGJ opening, outperformed the IRP on HRM to predict abnormal retention on TBE.[27] Consistent among these previous studies was that the FLIP study protocol and thresholds applied were all based on using metrics obtained during a stepwise *filling* protocol. Those thresholds were supported by normal values from healthy controls, as well as abnormal thresholds applied to consistently identify conclusive disorders of EGJ outflow, including achalasia.[23] Thus, at present, a limitation of emptying FLIP metrics is the lack of normative thresholds developed from testing of healthy, asymptomatic subjects.[10,20,21] Additionally, the present study demonstrated that a different threshold would need to be applied for identification of achalasia or relevant EGJOO if utilizing an emptying protocol of FLIP, and further, that doing so could actually increase overlap among patients with normal EGJ outflow on HRM and patients

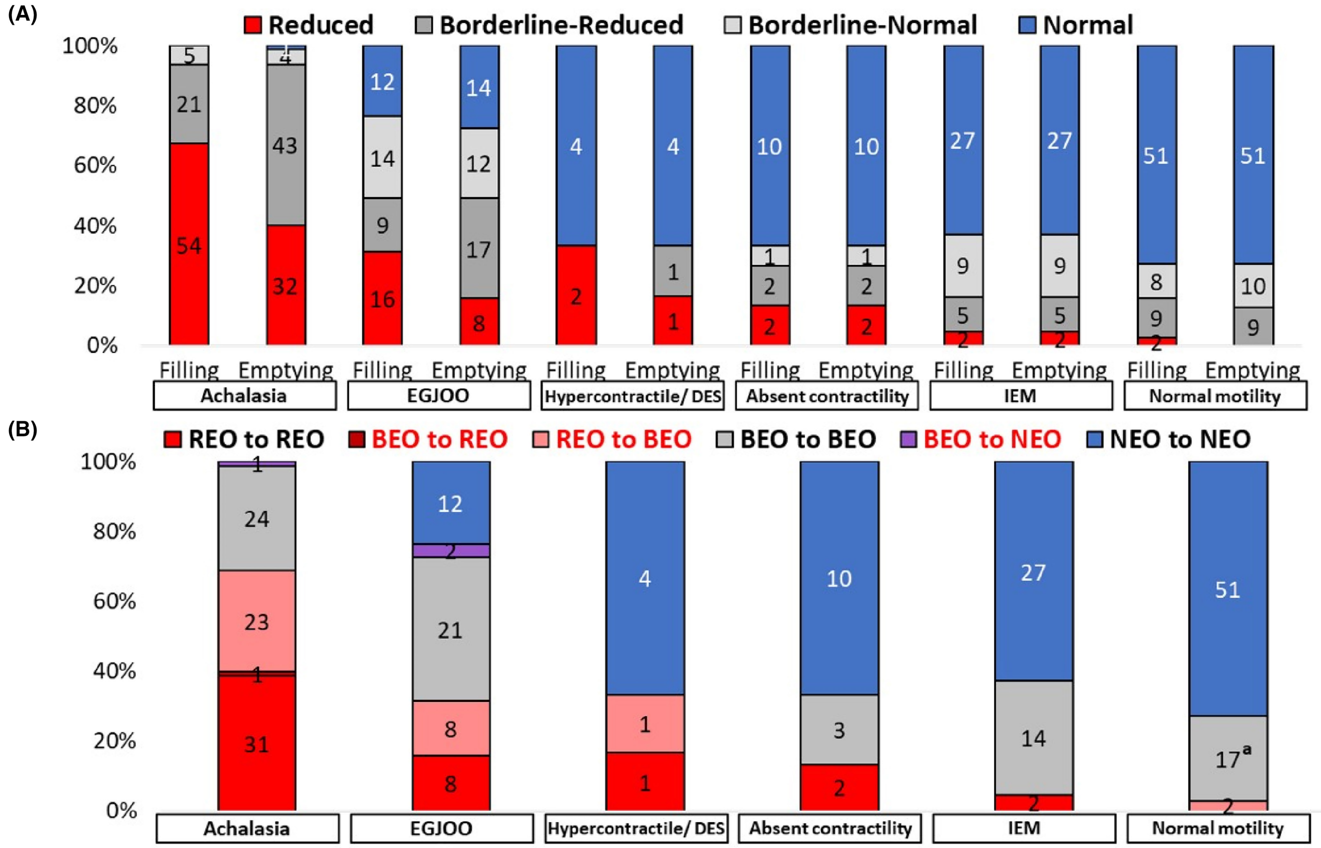

FIGURE 5 Impact of FLIP emptying on EGJ opening classification. (A) EGJ opening classification was defined using the EGJDI (60ml) and maximum EGJ diameter (60ml or 70ml) using the "filling" 60ml or "emptying" 60ml. (B) Rates of change (red text in legend) or stable EGJ opening classification from filling to emptying 60ml, respectively. Data labels indicate number of patients. aOnly two patients among the entire cohort changed from borderline reduced to borderline normal EGJ opening, both had normal motility. REO, reduced EGJ opening; BEO, borderline EGJ opening; NEO, normal EGJ opening; EGJOO, EGJ outflow obstruction; DES, distal esophageal spasm; IEM, ineffective esophageal motility.

with achalasia. Ultimately, volumetric FLIP filling (with measures during passive esophageal distension) and FLIP emptying (measures after reduced volume distension at passive shortening) represent different mechanical states and stimuli on the esophagus and thus elicit different physiomechanical responses at the LES. Thus, metrics from these different portions of the FLIP protocol (filling vs. emptying) should not be used interchangeably.

Despite the frequent benefits demonstrated with FLIP measures of EGJ distensibility to date, abnormal EGJ distensibility on FLIP can be observed among patients with normal EGJ outflow pressure (normal LES relaxation) on HRM.[8,9,28] While this abnormal response to distension may identify patients with pathology not detected by the standard HRM evaluation, it also could potentially cause clinical confusion based on the apparent discordance with HRM. Thus, we hypothesized that reduced volume distension with emptying of the FLIP bag might help improve identification of patients with clinically relevant reduced EGJ distensibility even if there were normal LES relaxation pressures on manometry. However, we instead observed that the response to emptying of the FLIP was somewhat similar in these patients as in patients with achalasia. Further, patients with normal motility or IEM on HRM that "normalized" EGJ opening parameters during emptying of the FLIP did not appear to differ from patients with consistently normal EGJ opening parameters, with the potential exception of a "spastic-reactive" contractile response being frequent in this scenario. Additionally, this response did not appear to be associated with presence of small hiatal hernia, as hypothesized as a potential associated factor in previous studies.[8,9] Overall, however, we did again observe that abnormal EGJ opening, particularly with a classification of REO, was rarely observed among patients with normal motility or IEM on HRM.

While this study is the first to focus on the physiologic response to reduced volume distension on FLIP relative to manometric motility diagnoses, a similar observation related to emptying of the FLIP was made in a previous study.[29] This previous study's experimental protocol included a standard 8-cm FLIP filling protocol (30 mL, 40 mL, then 50 mL) while the endoscope remained within the esophagus, and then removed the endoscope before retaking measures at 50 mL and after emptying the FLIP to 40 mL, then 30 mL. Similar to our study, they also found that EGJ-DI and EGJ cross-sectional area (diameter equivalent) increased, without a significant change in FLIP pressure, after removal of the endoscope and emptying to 40 mL and 30 mL fill volume. They also observed an increase in EGJ-DI with lower FLIP pressure after removal of the endoscope during the stable 50 mL-fill volume.

TABLE 3 Clinical associations with change in EGJ opening classification among patients with normal motility or ineffective esophageal motility (IEM) on high-resolution manometry (HRM).

EGJ-DI status	Normal	Reduced to normal	Normal to reduced	Reduced
Filling 60 mL EGJ-DI, mm^2/mmHg	≥2.0	<2.0	≥2.0	<2.0
Emptying 60 mL EGJ-DI, mm^2/mmHg	≥2.0	≥2.0	<2.0	<2.0
n (%)	97 (86)	9 (8)	3 (3)	4 (4)
Age, mean (SD), year	48.4 (16.1)	60.4 (14.8)	65 (12.7)	57.5 (7.8)
Sex, female, *n* (%)	70 (72.2)	6 (66.7)	1 (33.3)	2 (50)
BMI, mean (SD), kg/m^2	26.4 (6)	26.6 (4.4)	27.9 (0.5)	33.8 (2.7)
HRM-CCv4.0, *n* (%)				
Normal motility	59 (60.8)	7 (77.8)	2 (66.7)	2 (50)
IEM	38 (39.2)	2 (22.2)	1 (33.3)	2 (50)
Indication, *n* (%)				
Dysphagia	73 (75.3)	7 (77.8)	1 (33.3)	4 (100)
Reflux symptoms	13 (13.4)	1 (11.1)	1 (33.3)	0
Chest pain	5 (5.2)	0	0	0
Other (follow-up, preoperative)	6 (6.2)	1 (11.1)	1 (33.3)	0
Endoscopy findings, *n* (%)				
Erosive esophagitis (LA-A/B)	7 (7.2)	0	0	0
Nonobstructing ring	3 (3.1)	0	0	1 (25)
Diverticulum	3 (3.1)	0	1 (33.3)	0
Normal	84 (86.6)	9 (100)	2 (66.7)	3 (75)
Hiatal hernia (HRM), *n* (%)				
Present	56 (57.7)	4 (44.4)	0	2 (50)
Absent	41 (42.3)	5 (55.6)	3 (100)	2 (50)
Timed barium esophagram (TBE)				
Completed	38 (39.2)	5 (55.6)	2 (66.7)	2 (50)
1-min column height, mean (SD), cm	1.5 (3.8)	1 (2.3)	0	0
5-min column height, mean (SD), cm	0	0	0	0
Tablet impaction, *n* (%)	1 (1)	0	0	0
Abnormal TBE, *n* (%)	7 (7.2)	1 (11.1)	0	1 (25)
BEDQ				
Completed, *n* (%)	91 (80.5)	9 (100)	2 (66.7)	2 (50)
Score, mean (SD)	9.5 (9.5)	10 (8.8)	8 (1.4)	3 (4.2)
GerdQ				
Completed, *n* (%)	94 (83.2)	9 (100)	2 (66.7)	2 (50)
Score, mean (SD)	8.3 (2.8)	8.7 (3)	8.5 (3.5)	8.5 (3.5)
FLIP contractile response patterns, *n* (%)				
Normal	31 (32)	1 (11)	0	1 (25)
Borderline	20 (21)	0	2 (67)	0
Impaired disordered	29 (30)	4 (44)	0	1 (25)
Spastic-reactive	4 (4)	2 (22)	1 (33)	1 (25)
Absent	13 (13)	2 (22)	0	1 (25)

Abbreviations: BEDQ, Brief Esophageal Dysphagia Questionnaire; BMI, body mass index; CCv4.0, Chicago Classification version 4.0; LA, Los Angeles Classification.

While they hypothesized their findings represented distal inhibition of the LES that resulted from esophageal body distension generated by the endoscope presence, the results of our present study suggest that this may instead represent the response of the esophagus to the reduced volume distension from emptying of the FLIP. They did ultimately conclude that their findings supported the need for standardization of the FLIP protocol, which is further supported by the results of our present study.

While clear clinical benefits of including an emptying phase during a FLIP study protocol are not forthcoming from the present study, it does offer potential insights into the physiologic response assessed during the FLIP Panometry study. While there was an increase in EGJ-DI and EGJ diameter across the spectrum of esophageal motility disorders, the degree of the change in FLIP pressure was small (typically less than 3 mmHg), which suggests that the changes in LES dynamics in response to relief of distension are probably linked to isotonic relaxation (i.e., increased diameter without change in pressure) more so than auxotonic relaxation (i.e., increased diameter with reduced pressure).[30] Costa et al noted the uncertain mechanism underlying isotonic relaxation in intestinal muscle, though suggested that it was probably due to inhibitory neural input. However, given that this response was observed in achalasia patients, it supports that this isotonic relaxation occurs even when there is a defect in inhibitory neural function. Thus, excitatory pathways or intrinsic myogenic properties of the LES may be responsible for the observed response. Previously, it was demonstrated that focal balloon distension of the esophageal body induced LES relaxation in healthy controls (with restoration of LES pressure on deflation of the balloon), while in achalasia there was absence of LES relaxation and sometimes a paradoxical LES contraction.[31] This supported that the esophageal descending inhibitory pathway was defective in achalasia and is also reflected by the typical FLIP response in achalasia involving reduced EGJ distensibility. In patients with normal HRM, but abnormal FLIP, there could also be impairment in descending inhibitory pathways that may be uncovered on FLIP, but not HRM. This may be related to a defect in the triggering of descending inhibition, which may also be suggested by the association of abnormal contractile responses (i.e., lack of triggering secondary peristalsis). An association of EGJ opening with contraction response pattern was again observed in this study, including an effect on the LES response to FLIP distension versus reduced volume distension. Overall, future study, potentially to examine the effects of reduced volume distension relative to pharmacologic challenge, remain needed to clarify the mechanisms underlying this response.

While this study carries numerous strengths, including its novelty and sample size, there are limitations noted as well. One such limitation is the missingness of ancillary clinical results, such as patient reported outcomes and esophagrams, which limits determination of the clinical relevance of the associated FLIP findings in some cases. Additionally, this cohort reflects one evaluated in a quaternary referral center, and thus achalasia is overrepresented compared to what might be expected in a community practice setting. Thus, while this may limit generalizability, it may also have underestimated that potential improved diagnostic yield of utilizing an emptying phase in the FLIP study protocol. Finally, this study focused on achalasia, IEM, and normal motility based on our initial hypothesis for application of the emptying phase of the FLIP study, but did not expand at present onto its potential application to other HRM diagnoses. Thus, future study remains needed, though anticipated future directions include focus on CCv4.0 diagnoses, such as EGJOO and absent contractility. Additionally, further evaluation is warranted to determine if the variable responses to filling versus emptying on FLIP among achalasia has potential impact on prediction of longitudinal response to treatment.

In conclusion, the EGJ response to reduced volume distension (emptying of FLIP bag) generally involved an increase in EGJ-DI in an isotonic manner in patients with achalasia, as well as those with normal LES relaxation per HRM (e.g., CCv4.0 of normal motility and IEM). Thus, while we hypothesized that a FLIP protocol including emptying of the FLIP bag could clarify the scenario when there is an abnormal LES response to distension in patients with normal HRM-based LES relaxation, it ultimately appeared that its clinical impact to do so was low. Instead, however, the uninformed application of emptying EGJ FLIP metrics could result in a lowered yield to detect achalasia and relevant EGJ outflow obstruction. Thus, an important conclusion of this study is that diagnostic thresholds for application of FLIP metrics need to be consistently applied relative to the FLIP study protocol, and thus supports utilization of a standardized FLIP motility study protocol of controlled, 10 mL stepwise filling to 50 mL, 60 mL, then 70 mL (holding each volume for 30–60 s). Additionally, this study offers potential insights into the unique physiology represented by the FLIP Panometry study that prompts future investigation to determine whether the response to reduced volume distension have clinical relevance in other scenarios.

AUTHOR CONTRIBUTIONS

JWE contributed to drafting of the manuscript, data analysis, data interpretation, and approval of the final version. JEP contributed to study concept and design, data interpretation, obtaining funding, editing the manuscript critically, and approval of the final version. PJK contributed to data interpretation, critical revision of the manuscript, and approval of the final version. BG, DAF, and WK contributed to data analysis and approval of the final version. DAC contributed to drafting of the manuscript, study concept and design, data analysis, data interpretation, and approval of the final version.

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JEP: Sandhill Scientific/Diversatek (Consulting, Speaking, Grant), Takeda (Speaking), Astra Zeneca (Speaking), Medtronic (Speaking, Consulting, Patent, License), Torax (Speaking, Consulting), Ironwood (Consulting). PJK: Reckitt, Ironwood (consulting); Medtronic (License). DAC: Medtronic (Speaking, Consulting, License); Phathom Pharmaceuticals (Consulting), Braintree (Consulting); Medpace (Consulting). JWE, BG, DAF, WK: none.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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