Surg Endosc (2016) 30:2886–2894
DOI 10.1007/s00464-015-4574-2

Intraoperative measurement of esophagogastric junction cross-sectional area by impedance planimetry correlates with clinical outcomes of peroral endoscopic myotomy for achalasia: a multicenter study

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Received: 4 August 2015 / Accepted: 19 September 2015 / Published online: 20 October 2015

Abstract

Background Peroral endoscopic myotomy (POEM) has been introduced as an endoscopic alternative to surgical myotomy. The endoluminal functional lumen imaging probe (endoFLIP) evaluates esophagogastric junction (EGJ) distensibility based on cross-sectional area and pressure in response to volume distension. The aim of this study was to evaluate whether there is a correlation between endoFLIP measurements during POEM and postoperative clinical outcomes in terms of symptom relief and development of post-procedure reflux.

Methods We conducted a retrospective review of achalasia patients who underwent POEM and intraoperative endoFLIP at three tertiary centers. Patients were divided into two groups based on clinical response measured by Eckardt score (ES): good response (ES < 3) or poor response (ES ≥ 3). Post-procedure reflux was defined as the presence of esophagitis and/or abnormal pH study. EGJ diameter, cross-sectional area, and distensibility measured by endoFLIP were compared.

Results Of the 63 treated patients, 50 had good and 13 had poor clinical response. The intraoperative final EGJ cross-sectional area was significantly higher in the good-response group versus poor-response group; median (interquartile range): 89.0 (78.5–106.7) versus 72.4 (48.8–80.0) mm^2 [$p = 0.01$]. The final EGJ cross-sectional area was also significantly higher in patients who had reflux esophagitis after POEM: 99.5 (91.2–103.7) versus 79.3 (57.1–94.2) mm^2 [$p = 0.02$].

Conclusion Intraoperative EGJ cross-sectional area during POEM for achalasia correlated with clinical response and post-procedure reflux. Impedance planimetry is a potentially important tool to guide the extent and adequacy of myotomy during POEM.

Keywords Endoluminal functional lumen imaging probe · Esophagogastric junction · Peroral endoscopic myotomy · Achalasia

Abbreviations

CSA	Cross-sectional areas
ES	Eckardt score
endoFLIP	Endoluminal functional lumen imaging probe
EGJ	Esophagogastric junction
IQR	Interquartile range
IRP	Integrated relaxation pressure
LES	Lower esophageal sphincter

Electronic supplementary material The online version of this article (doi:10.1007/s00464-015-4574-2) contains supplementary material, which is available to authorized users.

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POEM Peroral endoscopic myotomy
SD Standard deviation

Background

Achalasia is an uncommon esophageal motility disorder characterized by loss of enteric neurons leading to impaired relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal body in response to swallowing. This pathophysiology results in impaired flow of ingested food into the stomach and stasis of food and secretions in the esophagus, which causes symptoms of dysphagia and regurgitation [1]. All available treatment options for achalasia—medical, endoscopic, and surgical—are palliative and directed at reduction in esophageal outflow obstruction.

Peroral endoscopic myotomy (POEM) has been introduced as an endoscopic alternative to surgical myotomy. Recent studies have shown that POEM is a highly effective treatment for achalasia in terms of symptomatic relief in medium-term follow-up and results in improvement of esophageal physiology [2–5]. The most common adverse event after POEM is gastroesophageal reflux. The prevalence of post-POEM abnormal esophageal acid exposure on ambulatory pH monitoring has been reported to be between 20 and 57 % [5–8].

Physiologic evaluation of esophagogastric junction (EGJ) opening, such as LES relaxation pressure on high-resolution manometry and bolus retention on timed barium esophagogram, can determine the post-treatment outcome in achalasia [9–11]; however, these tests are suboptimal. Intraoperative manometry [12, 13] is cumbersome and does not provide data on EGJ distensibility. Timed barium esophagogram cannot be used intraoperatively during the procedure.

A novel catheter-based tool, endoluminal functional lumen imaging probe (endoFLIP), uses impedence planimetry to assess EGJ geometry, physiology, and pressure in response to volume distension. Recent reports have shown that endoFLIP measurements can be helpful for evaluating efficacy of treatment for achalasia [10, 14]. This technology allows a real-time evaluation of the LES and EGJ during endoscopic or surgical procedures such as fundoplication [15] or esophagocardiomyotomy for achalasia [8, 16]. To date, there have been very limited data on the utility of intraoperative endoFLIP during POEM in predicting postoperative clinical outcomes.

The aim of this study was to evaluate whether there is a correlation between biomechanical parameters obtained from intraoperative impedance planimetry using endoFLIP during POEM and postoperative clinical outcomes in terms of symptom relief and development of post-procedure reflux.

Methods

We conducted a retrospective review of consecutive patients between the ages of 18 and 80 years with achalasia who underwent POEM and had intraoperative endoFLIP measurements between May 2013 and November 2014 at three tertiary care centers (two US and one European). Diagnosis of achalasia was based on the absence of esophageal peristalsis and impaired LES relaxation assessed with high-resolution manometry. Exclusion criteria included patients with high-resolution manometry consistent with diffuse esophageal spasm, Jackhammer esophagus or nutcracker esophagus and those with malignant or premalignant esophageal lesions. This study was approved by the Institutional Review Board for Human Research and complied with Health Insurance Portability and Accountability Act (HIPAA) regulations at each institution.

The following data were recorded: demographics, relevant clinical (Eckardt scores, previous endoscopic treatments), manometric (achalasia subtype, integrated relaxation pressure [IRP]), endoscopic data (length of submucosal tunnel, length of myotomy, orientation of myotomy), post-procedural clinical symptoms, results of upper endoscopy and esophageal acid exposure testing/pH-impedance testing after POEM.

POEM operative technique

POEM procedures were performed as previously described [17, 18]. In brief, a high-definition gastroscope, fitted with a transparent distal cap attachment, was used. Carbon dioxide insufflation was used during the entire length of the procedures, and intravenous antibiotics were administered. The lower esophageal sphincter (LES) was identified. A submucosal bleb was created in the mid-esophagus using saline mixed with indigo carmine. A 1.5- to 2-cm longitudinal mucosal incision was made with a triangular tip (TT) knife (KD 640L, Olympus, PA, US) using endocut mode at 50 W, effect 3 (ERBE, Tubingen, Germany). The endoscope was then maneuvered into the submucosal space. Spray coagulation mode (50 W, effect 2) or swift coagulation mode was applied to dissect the submucosal layer using the TT knife. The submucosal tunnel was extended, passing the LES and at least 2 cm into the proximal stomach. Subsequently, myotomy of the inner circular muscle bundles was performed starting 2 cm distal to the mucosal entry point using spray coagulation current at 50 W on effect 2 or swift coagulation mode. Larger vessels in the submucosa were coagulated using the Coagrasper (Olympus) in soft coagulation mode at 80 W on effect 5. Mucosal entry was then closed using endoscopic clips or endoscopic suturing.

Impedance planimetry

Intraoperative measurements were obtained using a commercially available endoFLIP system (Crospon Medical Devices, Galway, Ireland) and probes (EF-325 N). The probe consists of a 240-cm-long catheter with a 14-cm bag at its distal end. Within the bag, there is an 8-cm segment with 17 electrodes at 5-mm intervals inside the bag. Using impedance planimetry, cross-sectional areas are determined at the level of each electrode during volume control bag distensions. The probe also contains a pressure transducer that measures intrabag pressure. EndoFLIP measurements included EGJ diameter, cross-sectional areas (CSA), and distensibility. Distensibility was defined as the minimum CSA divided by the corresponding intrabag pressure. The balloon was inflated to a 30- and/or 40-ml volume.

The endoFLIP pressure sensor was zeroed before insertion of the probe. During POEM procedures and while patients were under general anesthesia, the endoFLIP probe was inserted through the patient's mouth. Under endoscopic visualization, the probe was advanced to the esophagus and positioned at the EGJ. EGJ CSA, diameter, and pressure were assessed at each distention volume using a median value during each 30-s test recording. The endoFLIP measurements were obtained at two time points: (1) baseline measurement before creation of the submucosal tunnel and (2) final measurement, after completion of the myotomy (Fig. 1).

Assessment of clinical outcomes

Symptom scores were assessed using the Eckardt score (ES) [19]. The components of the ES include weight loss, dysphagia, chest pain, and regurgitation. Each component is graded from 0 to 3. The final score is the sum of the four component scores, ranging from 0 to 12. In this study, the patients were classified based on post-procedure ES as having "good clinical response" if the ES < 3 or "poor clinical response" if the ES ≥ 3 [10].

The presence of objective evidence of abnormal esophageal acid exposure after POEM was defined as the presence of esophagitis (grade A or higher according to Los Angeles classification [20]) or abnormal pH study (DeMeester score >14.72 [21]). We routinely recommended POEM patients return for upper endoscopy, high-resolution manometry, and pH monitoring as part of routine follow-up at 3–6 months postoperatively. The pH monitoring test was performed while off PPI therapy for at least 1 week.

Outcome measures

We compared differences of intraoperative endoFLIP parameters between (1) clinical response: good-response group (ES < 3 after POEM) versus poor-response group (ES ≥ 3 after POEM); (2) post-procedure abnormal acid reflux: [2.1] patients with the presence of reflux esophagitis versus those without evidence of reflux esophagitis and [2.2] patients with abnormal pH study versus those with normal pH study.

Statistical analysis

Data were presented as frequencies and percentages, mean (standard deviation, ±SD) or median (IQR; interquartile

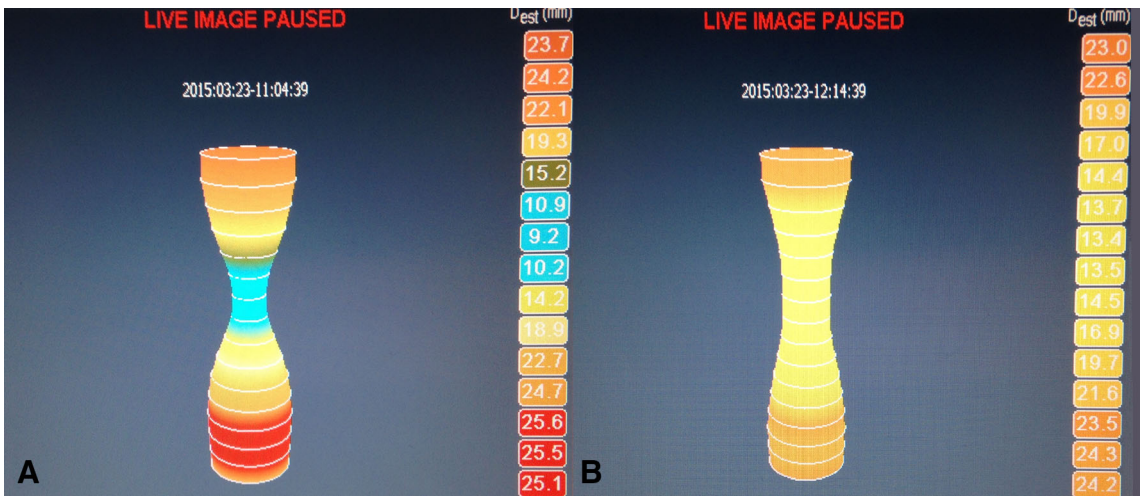

Fig. 1 Examples of endoFLIP displayed esophagogastric junction (EGJ) using a 40-ml volume distension, before (**A**) and after POEM (**B**), showing improvement of EGJ opening diameter after POEM. The narrowest diameter ("waist") corresponded with the EGJ opening. The corresponding cross-sectional areas (CSA) and intrabag pressure at that point were measured. EGJ distensibility (ratio between CSA and intrabag pressure) was based on the narrowest CSA and the corresponding intrabag pressure at each intrabag volume

range). Categorical data were compared by Fisher's exact test. Continuous data were compared by Student's t test or Mann–Whitney U test as appropriate. Comparisons of paired nonparametric data were tested by using the Wilcoxon signed-rank test. The optimal cutoff level of endoFLIP measurements in predicting clinical response was calculated from receiver operator characteristic analysis. Statistical analyses were conducted using SPSS software (SPSS 16.0, Chicago, IL). Two-sided p values <0.05 were considered significant.

Results

A total of 63 patients with achalasia [32 males (51 %); mean age 48.3 years] underwent POEM and intraoperative endoFLIP (13 type I, 42 type II, 5 type III, and 3 unspecified subtype). The pre-procedure median ES was 7 (IQR 6–9). A total of 29 (46 %) patients had received prior therapy: 11 botulinum toxin injections, 15 pneumatic dilations, 7 laparoscopic Heller myotomy and 5 POEM. Sigmoid esophagus was present in four patients.

The median follow-up after POEM procedure was 122 days (IQR 20–247). The median ES decreased from 7 (IQR 6–9) before POEM to 1 (IQR 0–2) after POEM ($p < 0.001$). Of these 63 patients, 50 (79 %) had ES < 3 (good-response group) and 13 patients (21 %) had ES ≥ 3 (poor-response group). Table 1 details the patient demographics, disease characteristics, and baseline high-resolution manometry measures. There were no significant differences between the two groups with respect to age, gender, race, body mass index, history of previous achalasia treatment, preoperative 4sIRP, baseline ES, achalasia subtype, and baseline endoFLIP measurements. Thirty-one patients (50 %) underwent high-resolution manometry after POEM procedure. Mean 4sIRP significantly decreased from 30.78 ± 2.9 mmHg before treatment to 13.46 ± 1.4 mmHg after treatment ($p < 0.001$).

Changes in endoFLIP profiles after POEM

The final endoFLIP measurements using 30- and 40-ml distension volumes were compared to the baseline measurements. At 30-ml volume distension, the final EGJ diameter and EGJ CSA data were available in all except one patient, whereas final EGJ distensibility was measured in 47 patients (68 %). The mean EGJ diameter and EGJ CSA significantly increased from 6.57 ± 1.60 to 10.49 ± 2.03 mm ($p < 0.001$) and 36.40 ± 19.35 to 88.5 ± 29.29 mm^2 ($p < 0.001$), respectively. The EGJ distensibility was significantly improved from 1.53 ± 1.09 mm^2/mmHg before myotomy to 4.75 ± 1.95 mm^2/mmHg after myotomy ($p < 0.001$).

At 40-ml volume distension, the final EGJ diameter and EGJ CSA data were available in 40 patients, whereas final EGJ distensibility was measured in 28 patients. The mean EGJ diameter and EGJ CSA significantly increased from 7.89 ± 2.15 to 13.15 ± 2.45 mm ($p < 0.001$) and 53.32 ± 28.97 to 142.32 ± 31.39 mm^2 ($p < 0.001$), respectively. The EGJ distensibility was significantly improved from 1.72 ± 1.66 mm^2/mmHg before myotomy to 6.22 ± 2.37 mm^2/mmHg after myotomy ($p < 0.001$).

EGJ biomechanical measurement and clinical response: good-response group versus poor-response group

Comparing the good-response group versus poor-response group, postoperative 4sIRP was significantly lower in the good-response group (11.7 mmHg ± 6.3 vs 18.3 ± 9.7, $p = 0.03$). The final EGJ diameter and EGJ CSA measured with 30-ml volume distension were significantly higher in the good-response group versus poor-response group: 10.9 (10.0–11.6) versus 9.9 (8.0–10.7) mm [$p = 0.03$] and 89.0 (78.5–106.7) versus 72.5 (48.8–80.0) mm^2 [$p = 0.01$], respectively. There was no significant difference in final EGJ distensibility using 30-ml volume distension between the two groups. At 40-ml volume distension, the endoFLIP measurements of EGJ diameter, CSA, and distensibility were not different between the two groups (Table 2).

Using receiver operator characteristic curve, the cutoff value of intraoperative final EGJ CSA > 80.0 mm^2 at 30-ml volume distension yielded sensitivity of 71 % and specificity of 84 % in predicting good clinical response after POEM (ES < 3) with an area under the curve of 0.74 ± 0.07 (Fig. 2). As shown in Fig. 3, 35 of 49 (71 %) cases in the good-response group had an intraoperative final EGJ CSA > 80 mm^2. This was in contrast to only 2 of 12 (16 %) cases in the poor-response group ($p = 0.001$).

EGJ biomechanical measurement and post-procedure acid reflux

Of 63 patients, 48 (76 %) had upper endoscopy and/or pH monitoring after POEM. There were no differences in the intraoperative final endoFLIP measurements between patients that did and did not have upper endoscopy and/or pH monitoring (Supplement Table A). Of the 48 patients, 21 patients (43 %) had evidence of esophagitis during upper endoscopy and/or abnormal esophageal acid exposure during pH monitoring.

Upper endoscopy was performed in 35 patients after POEM. Esophagitis was observed in 6 (17 %) patients (4 with grade A, 1 with grade B, and 1 with grade C esophagitis, according to the Los Angeles classification). Comparing patients with reflux esophagitis and those

Table 1 Comparison of achalasia patients based on treatment response

	Total ($n = 63$)	Good-response group ($n = 50$)	Poor-response group ($n = 13$)	p value
Age (mean ± SD; years)	48.3 ± 16.3	50 ± 16.6	41 ± 13.2	0.07
Male	32 (51 %)	26 (52 %)	6 (46 %)	0.76
Race				0.05
White	42 (66.7 %)	31 (65 %)	11 (84 %)	
Black	12 (19 %)	11 (23 %)	1 (8 %)	
Others	9 (14.2 %)	8 (16 %)	1 (8 %)	
Body mass index (mean ± SD)	26.3 ± 7.0	29.3 ± 16.2	25.7 ± 10.6	0.96
Previous treatment	29 (46 %)	22 (44 %)	7 (54 %)	0.55
Botulinum injection	11 (18 %)	10 (26 %)	1 (13 %)	
Pneumatic dilation	15 (24 %)	14 (37 %)	1 (13 %)	
Heller myotomy	7 (11 %)	5 (13 %)	2 (20 %)	
POEM	5 (6 %)	2 (5 %)	2 (22 %)	
Sigmoid esophagus	4 (6 %)	3 (8 %)	1 (13 %)	0.31
Preoperative IRP (mmHg)	36.5 ± 19.6	29.3 ± 16.1	25.7 ± 10.6	0.51
Preoperative Eckardt scores (median [IQR])	7 (IQR 6–9)	7.2 (IQR 7–9)	7 (IQR 5.5–8.5)	0.31
Achalasia subtypes				0.68
Type I achalasia	13 (20 %)	9 (18 %)	4 (31 %)	
Type II achalasia	42 (67 %)	35 (70 %)	7 (54 %)	
Type III achalasia	5 (8 %)	4 (8 %)	1 (8 %)	
Type, unspecified	3 (5 %)	2 (4 %)	1 (8 %)	
Baseline intraoperative endoFLIP measurement [median (IQR)]				
30-ml volume distension				
EGJ diameter (mm)	6.0 (5.2–7.2)	6.0 (5.2–7.2)	5.3 (5.0–7.2)	0.46
EGJ cross-sectional area (mm^2)	28.6 (21.2–40.7)	29.0 (21.2–41.3)	22.1 (19.8–40.7)	0.49
Bag pressure (mmHg)	27.1 (20.3–35.0)	27.5 (20.3–34.0)	27.1 (16.1–51.9)	0.89
Distensibility (mm^2/mmHg)	1.1 (0.75–1.94)	1.21 (0.7–2.1)	0.91 (0.73–1.46)	0.41
40-ml volume distension				
EGJ diameter (mm)	7.5 (5.8–9.0)	7.5 (5.8–9.1)	6.9 (5.5–7.9)	0.61
EGJ cross-sectional area (mm^2)	44.0 (28.0–65.0)	44.0 (26.5–65.0)	39.5 (29.0–68.0)	0.94
Bag pressure (mmHg)	44.0 (30.5–52.5)	38.0 (30.5–52.0)	54.6 (30.5–67.3)	0.23
Distensibility (mm^2/mmHg)	1.29 (0.67–1.86)	1.29 (0.67–1.87)	1.06 (0.49–1.46)	0.35
Procedural data				
Length of esophageal myotomy (cm) (mean ± SD)	8.65 ± 3.08	8.44 ± 3.22	9.46 ± 2.40	0.29
Length of gastric myotomy (cm) (mean ± SD)	3.06 ± 0.76	3.13 ± 0.78	2.77 ± 0.59	0.13
Orientation of myotomy				0.06
Anterior myotomy	48 (76 %)	41 (82 %)	7 (54 %)	
Posterior myotomy	15 (24 %)	9 (18 %)	6 (46 %)	

EGJ esophagogastric junction, *IQR* interquartile range, *IRP* integrated relaxation pressure, *POEM* peroral endoscopic myotomy

without reflux esophagitis, the final EGJ diameter and EGJ CSA at 30-ml distensions were significantly greater in those with reflux esophagitis: 11.2 (10.7–11.4) 10.1 (8.8–11.0) mm [$p = 0.03$] and 99.5 (91.2–103.7) versus 79.3 (57.1–94.2) mm^2 [$p = 0.02$], respectively. There was no significant difference in the final EGJ distensibility using 30-ml volume distension. At 40-ml volume distension, the endoFLIP measurements of EGJ diameter, CSA, and distensibility were not different between the two reflux groups (Table 3).

Of 19 patients who underwent postoperative pH monitoring, 16 (84 %) patients were considered to have abnormal acid exposure. The small number of patients precluded a meaningful comparison between the two groups.

Table 2 Comparisons between intraoperative endoFLIP measurement and treatment response [median (IQR)]

Final parameters	Good-response group (ES < 3)	Poor-response group (ES ≥ 3)	*p* value
30-ml volume distension			
EGJ diameter (mm)	10.9 (10.0–11.6)	9.9 (8.05–10.7)	0.03
EGJ cross-sectional area (mm^2)	89.0 (78.5–106.7)	72.4 (48.8–80.0)	0.01
Bag pressure (mmHg)	19.7 (15.4–23.5)	19.9 (11.7–26.1)	0.81
Distensibility (mm^2/mmHg)	4.83 (3.90–5.48)	3.34 (2.09–7.67)	0.15
Difference in EGJ diameter (mm)	4.7 (2.95–5.65)	2.7 (1.7–5.5)	0.26
Difference in cross-sectional area (mm^2)	59.0 (39.8–74.0)	25.8 (10.3–59.9)	0.03
Difference in bag pressure (mmHg)	−6.2 (−11.7 to −2.5)	−2.0 (−6 to −0.6)	0.22
Difference in distensibility (mm^2/mmHg)	3.41 (2.19–4.20)	1.77 (1.06–6.32)	0.36
40-ml volume distension			
EGJ diameter (mm)	13.5 (12.7–14.3)	14.0 (13.1–14.0)	0.67
EGJ cross-sectional area (mm^2)	145.0 (120.0–160.0)	153.0 (133.0–159.0)	0.69
Bag pressure (mmHg)	25.8 (19.9–28.6)	31.5 (13.3–56.7)	1.00
Distensibility (mm2/mmHg)	5.95 (4.55–8.90)	2.95 (1.00–9.90)	0.26
Difference in EGJ diameter (mm)	5.4 (3.8–7.4)	7.1 (5.1–8.4)	0.21
Difference in cross-sectional area (mm^2)	92.5 (57.0–123.2)	117.5 (68.0–123.5)	0.56
Difference in bag pressure (mmHg)	−14.1 (−19.0 to −4.3)	−11.1 (−31.2 to −8.5)	0.83
Difference in distensibility (mm^2/mmHg)	4.45 (2.7–5.25)	5.54 (2.22–8.64)	0.53

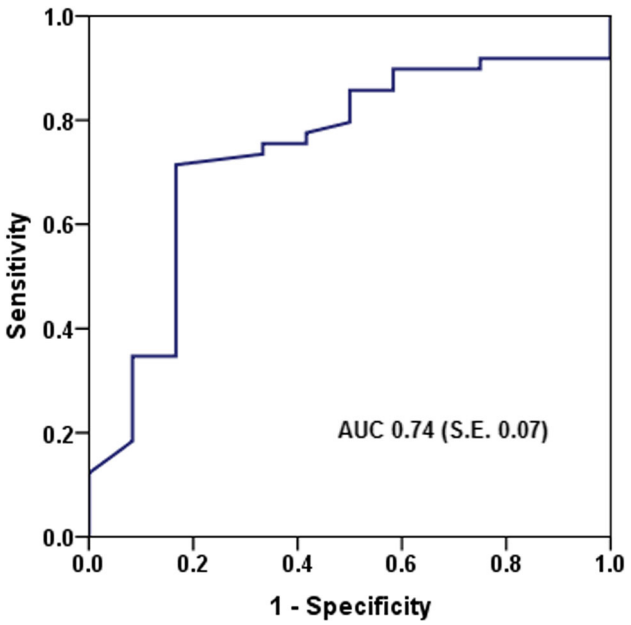

Fig. 2 The area under the concentration curve (AUC) of the EGJ cross-sectional area for predicting post-POEM clinical response

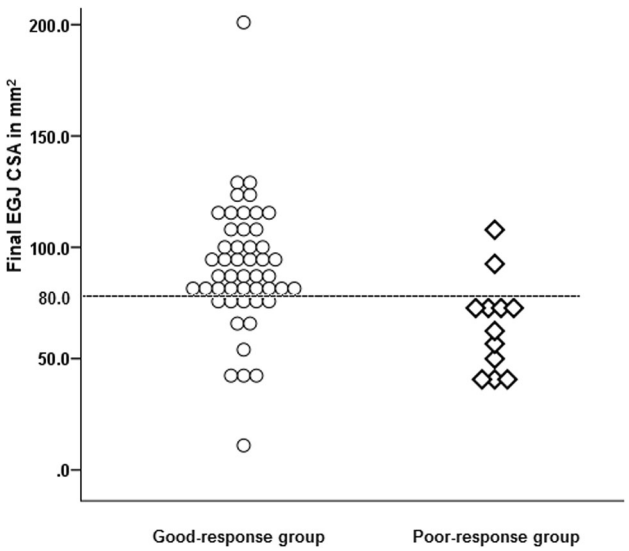

Fig. 3 Values for the intraoperative final EGJ cross-sectional area measured with 30-ml volume distension are compared for good-response group ($n = 49$) and poor-response group ($n = 12$). Using the cutoff value of EGJ CSA > 80.0 mm^2, 71 % of cases in good-response group and 16 % of cases in poor-response group were above this level; $p = 0.001$

Comparing the patients that had evidence of esophagitis during upper endoscopy and/or abnormal esophageal acid exposure during pH monitoring after POEM ($n = 21$) and those who had no evidence of esophagitis and/or abnormal esophageal acid exposure during pH monitoring ($n = 27$), the final EGJ diameter and EGJ CSA at 30-ml distensions were significantly higher in the patients with evidence of esophagitis during upper endoscopy and/or abnormal esophageal acid exposure during pH monitoring: 11.1

Table 3 Comparisons between intraoperative endoFLIP measurement and post-procedure reflux esophagitis [median (IQR)]

Final parameters	Presence of reflux esophagitis	Absence of reflux esophagitis	*p* value
30-ml volume distension			
EGJ diameter (mm)	11.2 (10.7–11.4)	10.1 (8.8–11.0)	0.03
EGJ cross-sectional area (mm^2)	99.5 (91.2–103.7)	79.3 (57.1–94.2)	0.02
Bag pressure (mmHg)	22.8 (14.3–37.6)	16.2 (14.2–19.7)	0.40
Distensibility (mm^2/mmHg)	4.9 (2.9–7.0)	4.8 (3.9–5.9)	0.82
Difference in EGJ diameter (mm)	5.1 (2.5–5.8)	4.0 (2.2–5.4)	0.41
Difference in cross-sectional area (mm^2)	66.0 (39.1–74.7)	55.0 (21.8–73.5)	0.41
Difference in distensibility (mm^2/mmHg)	2.3 (0.4–3.6)	3.4 (1.8–4.2)	0.15
40-ml volume distension			
EGJ diameter (mm)	14.2 (13.5–14.6)	13.0 (10.9–14.7)	0.35
EGJ cross-sectional area (mm^2)	160.0 (131.5–168.0)	134.0 (92.7–171.7)	0.43
Bag pressure (mmHg)	26.6 (20.6–51.8)	19.5 (15.8–25.5)	0.28
Distensibility (mm^2/mmHg)	6.8 (3.3–8.7)	8.9 (1.3–9.0)	0.67
Difference in EGJ diameter (mm)	5.5 (2.7–7.9)	6.3 (4.0–8.3)	0.63
Difference in cross-sectional area (mm^2)	100.0 (40.5–126.0)	105.0 (55.0–131.0)	0.63
Difference in distensibility (mm^2/mmHg)	2.2 (0.3–4.5)	8.1 (3.8–8.2)	0.19

(10.3–11.8) versus 9.9 (8.6–10.9) mm [$p = 0.04$] and 95.0 (83.0–110.0) versus 76.4 (52.0–89.0) mm^2 [$p = 0.01$], respectively. There was no significant difference in the final EGJ distensibility using 30-ml volume distension. At 40-ml volume distension, the endoFLIP measurement of EGJ diameter, CSA and distensibility were not different between the two groups.

Discussion

Our results indicate that POEM dramatically improved the physiology of esophagogastric function as shown by increasing EGJ diameter, EGJ CSA, and distensibility after the procedure. Moreover, intraoperative endoFLIP measurements correlated with treatment response and post-procedure reflux. Patients with lower final intraoperative EGJ CSA were more likely to have persistent symptoms after POEM, while higher final EGJ CSA was associated with post-procedure reflux.

POEM is a novel endoscopic procedure for the treatment of achalasia and aims to relieve resistance to passage of food at the EGJ via myotomy. EndoFLIP allows real-time assessment of EGJ physiologic changes including CSA, corresponding pressure, and EGJ distensibility. We noted an immediate improvement of EGJ CSA and distensibility after POEM. These findings agree with prior studies of intraoperative endoFLIP that demonstrated increases in EGJ CSA and EGJ distensibility after POEM [8, 22, 23].

Two previous studies have highlighted the utility of endoFLIP in the evaluation of achalasia patients after therapeutic interventions [10, 14]. Rohof et al. [14] demonstrated that EGJ distensibility was significantly higher in patients who were successfully treated with pneumatic dilation and/or laparoscopic Heller myotomy compared to patients who were treatment failures. Moreover, EGJ distensibility at 50-ml volume distension using the cutoff of 2.9 mm^2/mmHg had a sensitivity and specificity for predicting treatment failure of 92 and 72 %, respectively. Similar results were reported by Pandolfino et al. [10] where EGJ distensibility was significantly higher in achalasia patients with good clinical response after treatment with pneumatic dilation ($n = 10$), Heller myotomy ($n = 10$), or POEM ($n = 4$) than untreated patients or patients with poor treatment response.

Our results showed that the final EGJ CSA correlated with treatment response. Patients with intraoperative final EGJ CSA > 80.0 mm^2 were four times more likely to have good clinical response as compared to those with EGJ CSA < 80.0 mm^2. In contrast to previous studies [10, 14], we did not find correlation between EGJ distensibility and persistent symptoms in the postoperative period. However, it should be noted that our study aimed to evaluate the prognostic utilities of intraoperative endoFLIP measurement, whereas the endoFLIP values in previous reports were measured during an outpatient setting [10, 14]. EndoFLIP measurements obtained during the operation could have been different from the measurements obtained in the postoperative period due to many factors [15, 24, 25]. For

instance, Nathanson et al. [24] demonstrated that intraoperative endoFLIP measurements were significantly affected by the impact of pneumoperitoneum. In addition, we noted that post-treatment IRP was significantly lower in achalasia patients with good treatment response after POEM. This finding is consistent with previous studies [10, 11].

There have only been few studies assessing the utility of intraoperative endoFLIP during POEM [8, 16]. Teitelbaum et al. [16] reported that intraoperative EGJ distensibility was predictive of postoperative symptomatic outcomes in achalasia patients after surgical myotomy and POEM. Patients with a final EGJ distensibility of 4.5–8.5 mm^2/mmHg were twice as likely to have optimal symptomatic outcomes (defined by ES $\leq$ 1 and GERD symptoms score $\leq$7) as those outside this range. However, this particular study was limited by the fact that the authors combined data of patients who underwent surgical myotomy and POEM, and they relied on patients' report of GERD symptoms rather than objective evidence of abnormal esophageal acid exposure (e.g., EGD and/or follow-up pH study). A recent study of intraoperative endoFLIP by Familiari et al. [8] found no significant correlation between EGJ diameter measured with 30-ml balloon distension in 21 achalasia patients with ES of 0 and those with ES $>$ 0. Variability in the number of patients and the definition of clinical response in these studies and our study could explain the difference in results.

One of the most common adverse events after POEM is gastroesophageal reflux which has been reported to occur in 20–57 % of cases [5–8]. The role of endoFLIP in evaluating risk of gastroesophageal reflux after POEM is evolving, although the existing data are conflicting [8, 25, 26]. Kwiatek et al. [25] showed that EGJ distensibility in patients with reflux symptoms was twofold to threefold higher than that of controls. However, subsequent studies did not confirm these results [8, 26]. In our study, 43 % of patients had evidence of abnormal acid reflux on upper endoscopy and/or pH monitoring. We noted that achalasia patients with wider intraoperative final EGJ diameter and larger EGJ CSA were significantly more likely to have reflux esophagitis after POEM. Our results suggested that intraoperative EGJ CSA correlates with postoperative pathologic acid reflux.

A recent study suggested that intraoperative endoFLIP has the potential to act as a useful tool for myotomy calibration during POEM. Patients within an "ideal range" of endoFLIP values were more likely to have optimal outcomes in terms of symptom relief and minimal risk of iatrogenic reflux [16]. However, based on our results, there was considerable overlap in the final EGJ CSA of patients who had good clinical response and those who developed postoperative reflux [median (IQR): 89.0 (78.5–106.7) and 99.5 (91.2–103.7) mm^2, respectively]. This could mean that while effective myotomy during POEM provides excellent relief of dysphagia, patients are still at high risk of the development of post-POEM reflux.

The current study has some limitations. First, this was a non-randomized retrospective study from tertiary centers and some elements of clinical data as well as procedural information were not available. Second, our study was limited by a small sample size in each group as well as limited duration of follow-up time. However, a recent study showed that symptom relief after POEM is immediate and durable after an average follow-up of 11 months.[5]

In conclusion, intraoperative endoFLIP during POEM is a diagnostic tool that allows prediction of symptomatic response and post-procedure reflux after POEM. Patients with lower final intraoperative EGJ CSA were more likely to have persistent symptoms after POEM, whereas higher final EGJ CSA was associated with post-procedure gastroesophageal reflux. Further prospective studies with longer follow-up and higher number of patients are required to confirm our results and assess the impact of this technology on patient outcomes.

Compliance with ethical standards

Disclosures Mouen A. Khashab is a consultant for Boston Scientific, Olympus America, and Xlumena. Michel Kahaleh is a consultant for Boston Scientific and Xlumena and has done research for Gore, MI Tech, and Pinnacle. He has done research and consulting for Mauna Kea Technologies. Anthony N. Kalloo is a founding member, equity Holder, and consultant for Apollo Endosurgery. Burkhard H. A. von Rahden received travel grants by Karl Storz GmbH Tuttlingen for establishing the POEM procedure in Wuerzburg. Furthermore, POEM procedure with KARL STORZ GmbH equipment was funded by the company. Saowanee Ngamruengphong, Jörg Filser, Amy Tyberg, Amit Desai, Reem Z. Sharaiha, Arnon Lambroza, Vivek Kumbhari, Mohamad El Zein, Ahmed Abdelgelil, Sepideh Besharati, John O. Clarke, and Ellen M. Stein have no conflict of interest or financial ties to disclose.

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