

**SYMPTOM ASSOCIATION FOR GASTROESOPHAGEAL REFLUX DISEASE BY PH MONITORING
AFTER PERORAL ENDOSCOPIC MYOTOMY**

Short Title: GERD and symptoms after POEM

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Abbreviations: BMI: body mass index, CR: complete response, EGJ: esophagogastric junction, EGJOO: esophagogastric outlet obstruction, EGJ-DI: esophagogastric junction distensibility index, ES: Eckardt Score, FLIP: functional lumen imaging probe, HRM: high resolution esophageal manometry, IRP: integrated relaxation pressure, LES: lower esophageal sphincter; POEM: per-oral endoscopic myotomy

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Abstract

Introduction: There are limited data correlating symptoms with reflux episodes during pH studies after POEM.

Methods: Consecutive patients who underwent POEM followed ≥ 6 months later by 48-hour ambulatory wireless pH testing off antisecretory therapy were identified. Reflux symptom association (RSA) was defined as SAP $>95\%$.

Results: The most frequent of symptoms of heartburn (47.2%), cough (45.1%) and chest pain (39.6%) were associated with a positive RSA (SAP $>95\%$) in 20.9%, 17.1% and 19.4%, respectively.

Discussion: There is poor correlation between reported symptoms and esophageal acid exposure during pH testing after POEM.

Introduction

For patients with achalasia, there may be discordant objective findings and symptoms for GERD after myotomy of the lower esophageal sphincter (LES) [1]. Following peroral endoscopic myotomy (POEM), identification of GERD and associated reflux symptom association (RSA) is critical to triage patients to observation, antisecretory therapy, surgery, or alternative treatments. In this single center retrospective study of prospectively collected data, we evaluated consecutive patients who reported ≥ 1 symptom during wireless ambulatory pH monitoring ≥ 6 months after POEM. We hypothesized that symptoms would have limited correlation with objective esophageal acid exposure in these patients.

Methods and Materials

This IRB-approved study (ClinicalTrials.gov NCT02770859) enrolled consecutive patients between 2015 and 2019 who underwent POEM. Standard testing at baseline and ≥ 6 months after myotomy included high resolution impedance manometry (HRM), functional lumen imaging probe (FLIP) and Eckardt scores (ES). All patients were also offered 48-hour ambulatory wireless pH testing off antisecretory therapy ≥ 6 months after myotomy and those reported ≥ 1 symptom during pH testing comprise the primary study population.

HRM studies were performed with ten 5 mL liquid swallows in the supine position with additional upright swallows as required. During EGD and FLIP, EGJ distensibility index (EGJ-DI) at 40mL and 50mL distention was calculated [2]. All POEM procedures included myotomy approximately 2 cm into the gastric cardia when LES hypertension was

identified during baseline testing.

At 6-12 months after POEM, all were offered same day HRM, ES calculations, FLIP of the EGJ, and ambulatory wireless pH testing (Bravo™, Medtronic, Minneapolis, MN) off anti-secretory therapy for ≥ 7 days. Severity of any esophagitis was classified by the LA Classification [3]. Symptoms during pH testing were recorded and symptom index (SI) and symptom association probability (SAP) were calculated. Positive RSA for any symptom was defined as $SI \geq 50\%$ or $SAP > 95\%$ [4]. Conclusive, inconclusive, or absent GERD was determined by the Lyon criteria [5]. Inconclusive or absent GERD was negative for GERD.

Clinical response after POEM was defined by four metrics in the absence of a severe procedure-related adverse event or requirement for repeat LES-directed intervention: $ES \leq 3$ [6], $EGJ-DI > 2.8 \text{ mm}^2/\text{mmHg}$ at either 40ml or 50ml distention [7] and $IRP < 15 \text{ mmHg}$ [8].

Results

Of 300 consecutive patients who underwent POEM, 149 (49.7%) had pH testing ≥ 6 months after myotomy (Supplementary Figure 1 and Supplementary Table 1, <http://links.lww.com/AJG/C519>) and 91/149 (61%) reported ≥ 1 symptom (Table 1). Among these 91 patients, a median 11 symptoms (range: 1-191) were reported. A mean 8.8 ± 1.2 months after POEM, clinical response by ES, IRP, and EGJ-DI at 50 ml were 89%, 89.3% and 86.5% respectively. Post-POEM GERD occurred in 62/91 (68.1%).

The frequency of nine reported symptoms and correlation with acid exposure is shown in Table 2. The most frequent were heartburn (47.2%), cough (45.1%) and chest pain (39.6%). A positive RSA ($SAP > 95\%$) occurred in 20/91 (22%) and 20.9%, 17.1% and 19.4% reporting

heartburn, cough, and chest pain, respectively. The most frequent symptom with SAP>95% occurred in 9 of 43 (20.9%) reporting heartburn. Symptoms of epigastric pain, sore throat and belching did not have an RSA by SI or SAP in any patient. Among the 91 symptomatic patients, post-POEM GERD patients reported more frequent heartburn (56.4% vs. 27.6%, $p=0.013$) and had more severe esophagitis ($p=0.03$) compared to those without GERD (Table 3). A sensitivity analysis of RSA and total acid exposure stratified by a normal or elevated post-POEM IRP is shown in Supplementary Tables 2a and 2b, <http://links.lww.com/AJG/C519>.

Comparison among patients with ($n=20$) or without ($n=71$) at least one RSA (SAP >95%) is shown in Supplementary Table 3, <http://links.lww.com/AJG/C519>. Evaluation of the 149 patients with ($n=91$) or without ($n=58$) ≥ 1 symptom is shown in Supplementary Table 4, <http://links.lww.com/AJG/C519>. Among the 149 patients with pH testing, the diagnosis of GERD was similar between symptomatic (62/91, 68.1%) and asymptomatic (38/58 [65.5%], $p=0.86$) patients.

Discussion

In this study of 91 patients reporting ≥ 1 symptom during 48-hour pH testing ≥ 6 months after POEM, we found a positive RSA in 20/91 (22%) by SAP and 20.9%, 17.1% and 19.4% of the most common reported symptoms of heartburn, cough, and chest pain, respectively. These findings confirm recent data which found that post-POEM GERD patients have a much lower positive RSA (6%) compared to a control GERD group (56%, $p<0.001$) without achalasia [9]. Thus, the esophagus in patients with both treated and untreated [10] achalasia likely has a decreased sensitivity to acid exposure compared to normal patients.

Among the 91 symptomatic post-POEM patients, those with GERD reported more frequent heartburn and more severe esophagitis compared to those without GERD. Among all 149 receiving pH testing, any symptom was more likely to be reported by females and those with myotomies >9 cm. Importantly, the frequency of post-POEM GERD was similar between asymptomatic and symptomatic patients.

These findings add to recent literature about follow-up and testing after POEM. Esophagram < 24 hours after POEM does not predict clinical response or risk of GERD [11]. Furthermore, normal FLIP metrics by EGJ-DI are equivalent to a normal IRP by HRM to predict clinical response [12]. Finally, patient reported symptoms and preprocedural variables do not accurately predict development of post-POEM GERD [13]. Thus, EGD and FLIP off antisecretory therapy within 12 months of POEM may be used to test distensibility of the EGJ (and thus avoid HRM) and screen for esophagitis (to diagnose post-POEM GERD). If grade C or D esophagitis is present, then post-POEM GERD is confirmed [5]. However, for atypical symptoms or LA Grade A or B esophagitis, objective pH testing or an empiric PPI trial may be required.

The current study is the largest to date that reports RSA in consecutive patients during 48-hour pH testing ≥6 months after POEM. However, our study does have three important limitations. First, studies were reported only in patients during short-term follow up after POEM. Second, only 62% of all patients who underwent POEM during the study period had follow up pH studies. Finally, calculations of SI and SAP may be flawed even if positive since association of symptoms does not prove a definitive reproducibility of GERD and symptoms [14,15].

In conclusion, there is poor correlation between reflux symptoms and esophageal acid exposure following POEM. Therefore, objective testing by EGD, PPI trial or pH testing rather than patient reported symptoms may be required diagnose post-POEM GERD.

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Table 1: Baseline Demographics, POEM Characteristics, and Clinical Response in 91 Patients With ≥ 1 Reported Symptom During pH Monitoring ≥ 6 Months after POEM

Characteristic	Results (n, %)
Male	43/91 (47.3)
Mean (SD) BMI	29.6 (8.3)
Mean (SD) Age	55.0 (15.0)
Mean (SD) Esophageal Width (cm) (n=87)	3.2 (1.2)
Previous Therapy, n (%)	46/91 (49.5)
Botox injection	23/91 (25.3)
Pneumatic dilation	5/91 (5.5)
Heller myotomy	2/91 (2.2)
Other	16/91 (17.5)
Motility Disorder, n (%)	
Type 1 Achalasia	17/91 (18.7)
Type 2 Achalasia	42/91 (46.1)
Type 3 Achalasia	5/91 (5.5)
EGJ Outflow Obstruction	14/91 (15.4)
Hypercontractile Esophagus	8/91 (8.8)
Diffuse Esophageal Spasm	2/91 (2.2)
Other	3/91 (3.3)
Baseline Testing	
Mean (SD) Eckardt Score	7.4 (2.1)
Mean (SD) IRP (mmHg)	25.8 (15.5)
Mean (SD) EGJ-DI 40mL (mm ² /mmHg) (n=87)	1.2 (1.0)
Mean (SD) EGJ-DI 50mL (mm ² /mmHg) (n=72)	1.1 (0.9)
POEM Tunnel Location, n (%)	
Anterior	19/91 (20.9)
Posterior	63/91 (69.2)
Other	9/91 (9.9)
Myotomy Type, n (%)	
Circular Alone	54/91 (59.3)

Full Thickness	37/91 (40.7)
Myotomy Length, n (%)	
≤ 9 cm	40/91 (44.0)
> 9 cm	51/91 (56.0)
Clinical Response, n (%)	
Eckardt Score <3	81/91 (89.0)
IRP <15 mmHg (n=84)	75/84 (89.3)
EGJ-DI at 40mL >2.8 mm ² /mmHg (n=90)	84/90 (93.3)
EGJ-D at 50mL >2.8 mm ² /mmHg (n=89)	77/89 (86.5)
Post-POEM GERD, n (%)	62/91 (68.1%)

Table 1 Abbreviations: BMI: Body mass index; LES: lower esophageal sphincter; EGJ: esophagogastric junction, EGJ-DI: esophagogastric junction distensibility index (EGJ-DI); IRP: integrated relaxation pressure ; POEM: peroral endoscopic myotomy

Table 2: Frequency of Reported Symptoms and Correlation with GERD Events by Symptom Index (SI) and Symptom Associated Probability (SAP) during Ambulatory pH Monitoring Among 91 Patients who Reported At Least One Symptom During Testing

Reported Symptom	Overall Frequency Reported (%)	SI by Reported Symptom (%)	Mean SI by Reported Symptom (%)	Frequency SI \geq 50% by Reported Symptom	Mean SAP by Reported Symptom (%)	Frequency SAP >95% by Reported Symptom
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Footnote: Positive reflux symptom association for any symptom was defined as SI \geq 50% or SAP >95%

Heartburn	43/91 (47.2%)	108/441 (24.5%)	27.7	10/43 (23.3%)	42.7%	9/43 (20.9%)
Cough	41/91 (45.1%)	153/805 (19.0%)	18.2	7/41 (17.1%)	40.9%	7/41 (17.1%)
Chest pain	36/91 (39.6%)	149/528 (28.2%)	25.1	10/36 (27.8%)	41.3%	7/36 (19.4%)
Dysphagia	25/91 (27.5%)	40/246 (16.3%)	18.4	6/25 (24.0%)	31.8%	3/25 (12.0%)
Nausea	11/91 (12.1%)	6/116 (5.2%)	10.4	1/11 (9.1%)	21.1%	0/11 (0.0%)
Regurgitation	13/91 (14.3%)	42/80 (52.5%)	28.6	5/13 (38.5%)	38.9%	2/13 (15.4%)
Epigastric pain	7/91 (7.7%)	2/15 (13.3%)	5.7	0/7 (0.0%)	11.4%	0/7 (0.0%)
Sore Throat	5/91 (5.5%)	1/18 (5.6%)	2.9	0/5 (0.0%)	12.1%	0/5 (0.0%)
Belching	3/91 (3.3%)	1/14 (7.1%)	5.6	0/3 (0.0%)	22.1%	0/3 (0.0%)
				Frequency SI>50% in Patients Reporting at Least One Symptom		Frequency SAP >95% in at least one Symptom
Any Symptom	91/91 (100.0%)			30/91 (33.0%)		20/91 (22.0%)

Table 3: Frequency of Reported Symptoms and LA Classification of Esophagitis among those with (n=62) and without (n=29) GERD following POEM

Reported Symptom n (%)	Post-POEM GERD		
	Yes (n=62)	No (n=29)	P-value
Heartburn	35/62 (56.4%)	8/29 (27.6%)	0.013
Nausea	6/62 (9.7%)	5/29 (17.2%)	0.318
Chest pain	25/62 (40.3%)	11/29 (37.9%)	1.000
Sore Throat	5/62 (8.1%)	0/29 (0.0%)	0.173
Cough	25/62 (40.3%)	16/29 (55.2%)	0.258
Epigastric pain	3/62 (4.8%)	4/29 (13.8%)	0.203
Belching	3/62 (4.8%)	0/29 (0.0%)	0.549
Regurgitation	6/62 (9.7%)	7/29 (24.1%)	0.105
Dysphagia	17/62 (27.4%)	8/29 (27.6%)	1.000
Esophagitis LA Grade			0.030
None	14/62 (22.6%)	13/29 (44.8%)	
A	13/62 (21.0%)	7/29 (24.1%)	
B	21/62 (33.9%)	9/29 (31.0%)	
C	11/62 (17.7%)	0/29 (0.0%)	
D	3/62 (4.8%)	0/29 (0.0%)	

Footnote: GERD diagnosed by the Lyon Classification and reported as positive or negative (negative or equivocal)

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