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Loss of Inspiratory Augmentation as a Predictive Factor for the Development of Gastroesophageal Reflux Disease After Peroral Endoscopic Myotomy in Patients With Achalasia

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Background/Aims: Gastroesophageal reflux disease (GERD) after peroral endoscopic myotomy (POEM) is a significant challenge. Disruption of the lower esophageal sphincter during POEM and dysfunction of the crural diaphragm, which contributes to esophagogastric junction pressure, may lead to GERD after POEM. We aim to identify predictors of GERD after POEM and focus on physiological parameters of esophagogastric junction pressure in patients with achalasia before POEM.

Methods: We retrospectively analyzed a prospectively collected database of patients who underwent POEM between July 2016 and August 2023. Ninety-two patients with achalasia who underwent high-resolution manometry and endoscopy before and after POEM were included.

Results: Forty-nine (53.3%) patients were diagnosed with GERD. Patient demographics, achalasia subtypes, prior treatments, myotomy length, and myotomy orientation were not associated with GERD after POEM. Loss of inspiratory augmentation before POEM was associated with GERD after POEM ($P < 0.05$). GERD occurred more frequently in patients with a shorter intra-abdominal lower esophageal sphincter length before POEM. Type III esophagogastric junction morphology in the GERD group (37.1%) was more common than that in the non-GERD group (15.8%). Loss of inspiratory augmentation occurred more frequently in patients with type III esophagogastric junction pressure morphology.

Conclusion: Loss of inspiratory augmentation may predict GERD after POEM.

Keywords: Esophageal achalasia; Esophagogastric junction; Gastroesophageal reflux; Manometry; Myotomy

INTRODUCTION

Peroral endoscopic myotomy (POEM) is a minimally invasive endoscopic treatment for achalasia that provides excellent clinical outcomes and restoration of esophageal morphology and function.[1,2] However, the development of gastroesophageal reflux disease (GERD) after POEM has been a major concern since its introduction.[3] Meta-analyses have shown that GERD development after POEM is common. Symptomatic GERD occurs in approximately 19.0%, abnormal esophageal acid exposure occurs in approximately 39.0%, and erosive esophagitis occurs in approximately 20.0-30.0% of all patients after POEM. Notably, GERD rates after POEM are consistently higher than those after laparoscopic Heller myotomy with fundoplication.[4] The absence of an anti-reflux mechanism after myotomy, full-thickness myotomy, a posterior approach, and gastric myotomy longer than 2.5 cm are known contributors to GERD after POEM.[5]

Two critical components of the anti-reflux barrier of the esophagogastric junction (EGJ) are the internal lower esophageal sphincter (LES), which comprises smooth muscle, and external LES, which comprises skeletal muscle of the crural diaphragm (CD) and the phrenoesophageal ligament. The LES generates sustained or tonic contraction, whereas CD contraction increases LES pressure during inspiration.[6] EGJ pressure morphology is classified into 3 subtypes based on the axial relation-

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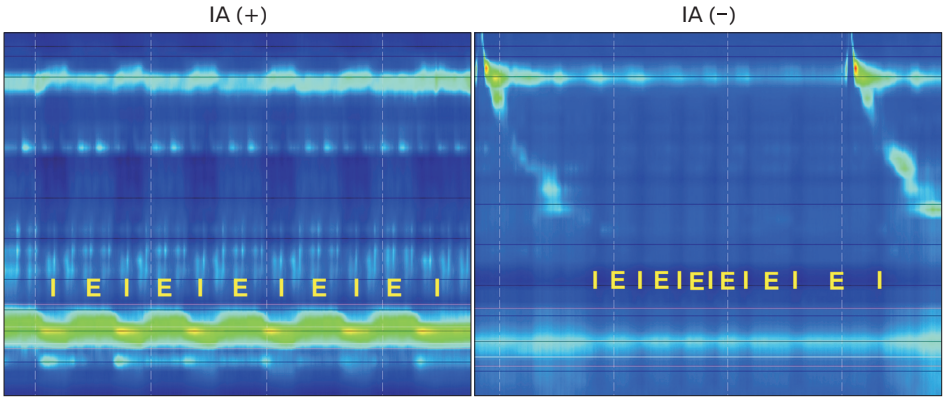

Figure 1. Inspiratory augmentation (IA). Esophagogastric junction pressure during inspiration exhibits a 10% increase compared with that during expiration. I, inspiration; E, expiration.

ship between the maximal EGJ pressure and CD pressure peaks during normal inspiration. Inspiratory augmentation, which is an indicator of the functional integrity of the CD, is considered protective against GERD[7] (Fig. 1).

We hypothesize that CD dysfunction may contribute to GERD after POEM in patients with achalasia. Therefore, in this study, we investigate novel predictors of GERD after POEM in patients with achalasia and focus on physiological EGJ pressure parameters before POEM.

MATERIALS AND METHODS

Study Participants

In this retrospective study, we analyzed prospectively collected data of 92 patients with achalasia who underwent POEM between July 2016 and August 2023. All patients underwent high-resolution manometry (HRM) and esophagogastroduodenoscopy before and after POEM. Achalasia was diagnosed based on clinical symptoms, barium esophagogram results, and HRM results according to the Chicago classification version 3.0.[8] Preoperative reflux esophagitis was absent in all patients. GERD status was assessed 6 months after the procedure. Proton pump inhibitors (PPIs) were selectively prescribed only for patients who experienced significant GERD-related symptoms after POEM. However, for these patients with GERD-related symptoms after POEM, PPIs were withheld for at least 1 month before the follow-up endoscopic evaluation when clinically tolerable to avoid underestimation of reflux esophagitis caused by mucosal healing. Patients with persistent or severe symptoms were evaluated earlier at the discretion of the treating physician. GERD was defined as either endoscopically documented reflux esophagitis (Los Angeles classification grade A or higher) or new-onset GERD symptoms (such as heartburn or regurgitation) severe enough to require PPI therapy. We compared EGJ physiological parameters of the GERD and non-GERD groups before POEM. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine (IRB no. 3-2025-0087). The requirement for individual informed consent was waived because of the retrospective design of the study.

High-resolution Manometry

HRM was performed by advancing a 36-channel solid-state probe system with high-fidelity circumferential sensors (Manoscan; Sierra Scientific Instruments Inc, Los Angeles, CA, USA) at 1-cm intervals into the nasal canal. Measurements were performed with the patient in the supine and sitting positions after fasting for at least 8 hours. Pressure data of 10 wet swallows were recorded and analyzed using the Manoscan 360 (Sierra Scientific Instruments Inc). All relevant measurements were obtained according to the Chicago classification version 3.0.[8] We defined inspiratory augmentation as a 10.0% increase in EGJ pressure during inspiration compared with that during expiration, as previously described by Pandolfino et al.[7] The EGJ of each individual was classified into one of 3 subtypes based on the axial relationship between the maximal EGJ pressure and CD pressure peaks during normal inspiration.[7] Type I referred to complete overlap of the CD and LES with a single pressure peak during both inspiration and expiration. Type II referred to a minimal, but visible, separation between the LES and CD. Type III, which is an indicator of hiatal hernia on HRM images, referred to a separation of > 2 cm between the LES and CD during inspiration.

Peroral Endoscopic Myotomy Procedure

POEM was performed under general anesthesia with endoscopic CO_2 insufflation, as described by Inoue et al.[9]

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First, 10 mL of saline solution with 0.3% indigo carmine was injected in the submucosal space 7-9 cm proximal to the EGJ. Subsequently, a 2-cm longitudinal mucosal incision was made using a Triangle Tip electrosurgical knife (KD-640L; Olympus, Tokyo, Japan) to create a mucosal entry into the submucosal space. The submucosal layer was dissected to create a tunnel along the esophagus and across the EGJ that extended 3 cm into the proximal stomach. Endoscopic myotomy of the circular muscle was initiated 2 cm below the tunnel entry (median, 5 cm) and extended 2 to 3 cm into the proximal stomach. Finally, the mucosal entry site was closed with endoscopic clips (EZ-CLIP; Olympus).

Statistical Methods

To compare variables of the non-GERD and GERD groups, Levene's test was conducted using the Levene test function of the *car* package (version 3.1-2) to assess the homogeneity of variance of continuous variables. Based on the results of Levene's test, either Student's *t* test or Welch's *t* test was performed using the one-way test function of the *stats* package (version 4.2.2).

Categorical variables were analyzed using the chi-squared test unless > 20% of cells had expected frequencies < 5; in that case, Fisher's exact test was used to analyze these variables. Both tests were conducted using the fisher.test and chisq.test functions of the *stats* package (version 4.2.2). All statistical analyses were performed using R software (version 4.2.2; The R Foundation, Vienna, Austria).

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.

RESULTS

Demographics

The demographics of the study population are presented in Table 1. Of the 92 patients included in this study, 42 (45.7%) had reflux esophagitis identified during follow-up esophagogastroduodenoscopy, and 7 (7.6%) had new GERD symptoms that necessitated PPI therapy initiation. Therefore, a total of 49 (53.3%) patients met our criteria for GERD. Among the 42 patients with endoscopy-proven reflux esophagitis, three reported typical reflux symptoms; however, the majority of these patients were asymptomatic. All 7 patients with non-erosive reflux disease were symptomatic. No patient exhibited reflux esophagitis on endoscopy before POEM, and POEM failure did not occur. All patients experienced symptomatic improvement after POEM. Our cross-sectional comparisons did not show significant differences in patient-related demographic factors, achalasia subtype, prior treatments, myotomy length, and myotomy orientation between the GERD and non-GERD groups (Table 1). However, these results were based on unadjusted analyses and should be interpreted with caution.

Manometric Factors Before Peroral Endoscopic Myotomy That Predict the Development of Gastroesophageal Reflux Disease After Peroral Endoscopic Myotomy

After excluding those in whom the HRM catheter could not traverse the EGJ, thus preventing identification of the respiratory inversion point, the data of 78 of the 92 patients with achalasia were analyzed. Loss of inspiratory augmentation on HRM before POEM was observed in 14

Table 1. Patient Demographics (N = 92)

Variables	Normal (n = 43)	GERD (n = 49)	*P*-value
Age (≥ 50 yr)	26 (60.5)	21 (42.9)	0.092
Age (yr)	52.0 ± 17.7	45.3 ± 16.0	0.061
Male	24 (55.8)	25 (51.0)	0.646
Body mass index (kg/m^2)	22.6 ± 3.6	23.0 ± 3.7	0.614
Achalasia			
Type I	7 (16.3)	11 (22.4)	0.269
Type II	20 (46.5)	24 (49.0)	
Type III	7 (16.3)	2 (4.1)	
Undetermined	9 (20.9)	12 (24.5)	
Previous treatment	9 (20.9)	14 (28.6)	0.398
Myotomy length (cm)			
Total length	9.0 ± 2.9	8.5 ± 2.5	0.349
Esophageal side	6.8 ± 2.8	6.1 ± 2.7	0.234
Gastric side	2.1 ± 1.2	2.4 ± 1.1	0.349
Myotomy position - anterior	25 (58.1)	30 (61.2)	0.763

GERD, gastroesophageal reflux disease.
Undetermined subtype: includes patients who underwent peroral endoscopic myotomy without pre-procedural high-resolution manometry (n = 9) or those treated for other esophageal motility disorders such as esophagogastric junction outflow obstruction, ineffective esophageal motility, or jackhammer esophagus (n = 12).
Previous treatment: includes botulinum toxin injection, pneumatic dilatation, pharmacologic treatment, smooth muscle relaxants, or surgical myotomy.
Data are presented as n (%) or mean ± SD.

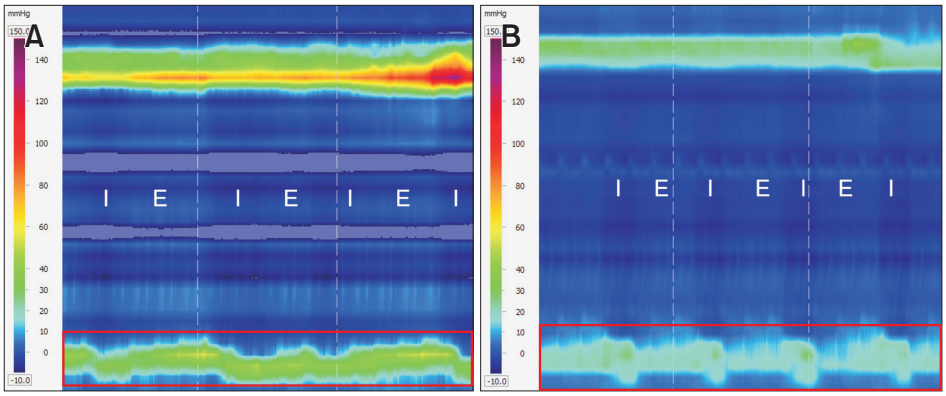

Figure 2. Representative high-resolution manometry image showing the absence of inspiratory augmentation before peroral endoscopic myotomy (POEM; A); however, inspiratory augmentation was restored after POEM (B). Inspiratory augmentation is highlighted in the red box. I, inspiration; E, expiration.

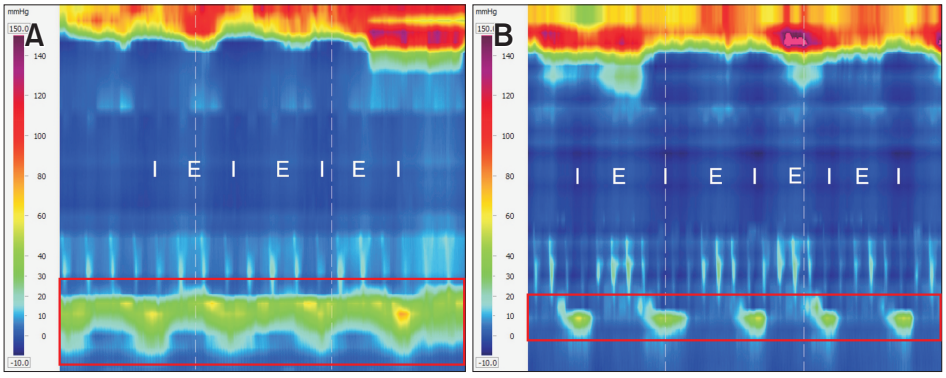

Figure 3. Representative high-resolution manometry image showing preserved inspiratory augmentation before peroral endoscopic myotomy (POEM; A) that remained preserved after POEM (B). Inspiratory augmentation is highlighted in the red box. I, inspiration; E, expiration.

of those 78 patients (17.9%) (12 in the GERD group and 2 in the non-GERD group). Additionally, loss of inspiratory augmentation on HRM images before POEM in the GERD group was significantly more frequent than that in the non-GERD group (30.0% vs 5.3%; $P = 0.011$). Therefore, loss of inspiratory augmentation before POEM was associated with GERD ($P < 0.05$). Some patients without inspiratory augmentation before POEM exhibited restored augmentation during follow-up HRM (Fig. 2 and 3). Notably, the reverse pattern was not observed; in other words, no patient with intact inspiratory augmentation before POEM demonstrated loss of augmentation after POEM. A subset of patients without inspiratory augmentation before POEM exhibited restored augmentation during follow-up HRM. Specifically, 9 patients demonstrated restoration, and 7 of those patients were in the GERD group. Although this finding suggested a trend toward more frequent restoration in patients with GERD, the association was not statistically significant ($P = 0.155$). Therefore, restoration of inspiratory augmentation may not always confer protection against GERD after POEM. Additionally, this phenomenon may reflect unmasking of inspiratory augmentation after reduction of the LES tone rather than true recovery of the CD function. Additionally, GERD was more common in patients with a shorter intra-abdominal LES length observed during HRM before POEM; however, the difference was not statistically significant ($P = 0.070$) (Table 2).

Table 2. Pre-peroral Endoscopic Myotomy Predictive Factors for Gastroesophageal Reflux Disease

Variables	Normal (n = 38)	GERD (n = 40)	*P*-value
Loss of inspiratory augmentation	2 (5.3)	12 (30.0)	0.011
Pre-POEM LES length (cm)	3.66 ± 0.77	3.45 ± 0.81	0.256
Pre-POEM intra-abdominal LES length (cm)	3.05 ± 0.72	2.73 ± 0.77	0.070

GERD, gastroesophageal reflux disease; POEM, peroral endoscopic myotomy; LES, lower esophageal sphincter.
Data are presented as n (%) or mean ± SD.

Esophagogastric Junction Pressure Morphology Before Peroral Endoscopic Myotomy and the Development of Gastroesophageal Reflux Disease After Peroral Endoscopic Myotomy

EGJ pressure morphology was identified in 73 of 78 patients with evaluable inspiratory augmentation (38 in the non-GERD group and 35 in the GERD group); the other 5 patients had HRM recordings that were technically

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Table 3. Types of Esophagogastric Junction Pressure Morphology in Pre-peroral Endoscopic Myotomy and Development of Gastroesophageal Reflux Disease (N = 73)

Characteristics	Normal (n = 38)	GERD (n = 35)	*P*-value
EGJ pressure morphology			0.116
Type I	22 (57.9)	15 (42.9)	
Type II	10 (26.3)	7 (20.0)	
Type III	6 (15.8)	13 (37.1)	

GERD, gastroesophageal reflux disease; EGJ, esophagogastric junction.
Data are presented as n (%).

Table 4. Esophagogastric Junction Pressure Morphology and Loss of Inspiratory Augmentation Pre-peroral Endoscopic Myotomy

	EGJ pressure morphology			*P*-value
	Type I	Type II	Type III	
Inspiratory augmentation				0.084
(+)	31	17	14	
(−)	6	0	5	

EGJ, esophagogastric junction.

inadequate and did not allow morphology classification. Among these 73 patients, type III EGJ morphology was observed in 37.1% of those in the GERD group and 15.8% of those in the non-GERD group (Table 3). Although patients with type III EGJ morphology more frequently experienced GERD development after POEM, the difference between groups was not statistically significant (*P* = 0.116). Additionally, loss of inspiratory augmentation was more common in patients with type III EGJ pressure morphology; however, the difference between groups was not statistically significant (*P* = 0.084) (Table 4).

DISCUSSION

In this study, we hypothesized that CD dysfunction before POEM may play a role in the development of GERD after POEM. We analyzed inspiratory augmentation of EGJ pressure as an indicator of the functional integrity of the CD and found that patients who experienced loss of inspiratory augmentation developed GERD after POEM more frequently. Furthermore, loss of inspiratory augmentation before POEM was independently associated with GERD after POEM.

To the best of our knowledge, this is the first study to identify a relationship between loss of inspiratory augmentation and GERD development after POEM in patients with achalasia.

Although LES pressure reduction via myotomy relieves symptoms, it may also increase distal esophageal acid exposure and promote symptomatic GERD. Consequently, previous studies have primarily focused on procedural factors such as the myotomy length or position as contributors to GERD after POEM in patients with achalasia.[10,11] Myotomy performed in the anterior position (2 o'clock) targets the lesser curvature of the stomach, which anatomically avoids the gastric sling fibers; in contrast, posterior myotomy may increase the disruption of sling fibers, thus potentially increasing the development of GERD after POEM. Despite this difference, in our study, neither the myotomy length nor the myotomy position influenced GERD development after POEM. This finding aligns with those of prior randomized controlled trials and meta-analyses that reported no significant differences in the GERD incidence with anterior myotomy and posterior myotomy.[12,13]

Although an elevated Eckardt symptom score and preoperative esophagitis have been correlated with GERD after POEM, the patient-related clinical factors assessed during our study, including age, sex, body mass index, achalasia subtype, previous treatments, myotomy length, and myotomy position, were not significantly associated with GERD after POEM.[14] However, our analysis included only a restricted number of clinical parameters (Table 1); therefore, other unexplored patient-related factors may significantly contribute to GERD development after POEM. Further studies that incorporate broader clinical parameters are warranted.

In addition to the smooth muscle of the internal LES, the external LES, which includes the skeletal muscle of the CD and phrenoesophageal ligament, plays a critical role in the EGJ anti-reflux barrier. CD contraction increases EGJ pressure during inspiration, and inspiratory augmentation, which is a marker of CD integrity, is a protective factor against GERD.[7,15] In our study, all patients who exhibited intact inspiratory augmentation before POEM also experienced preserved inspiratory augmentation after POEM, suggesting that POEM does not impair CD function. Conversely, some patients without inspiratory augmentation before POEM exhibited intact augmentation after POEM on HRM images. This may have occurred because the influence of inspiration on EGJ pressure may have been masked, even if the CD function was intact, in patients with a markedly elevated LES tone. Upon reduction in the LES tone after POEM, inspiratory augmentation could be unmasked, reassessed, and classified as intact. Notably, some patients without inspiratory augmentation

before POEM exhibited restoration after POEM, and most of those patients were in the GERD group. This finding suggests that restoration of inspiratory augmentation does not always confer protection against GERD; instead, it may reflect unmasking of diaphragmatic contraction after LES tone reduction, consistent with the findings of prior studies of the role of the CD function in modulating EGJ pressure.[6,7,16]

Recently, Mittal et al[16] demonstrated that the replacement of fat with fibrous tissue around the LES significantly contributes to reduced LES compliance in achalasia. In the present study, 17.9% of patients exhibited impaired inspiratory augmentation. However, whether the prevalence of impaired inspiratory augmentation differs between patients with achalasia and those without achalasia is unclear because few studies have reported its prevalence in the general population. Further research is warranted to elucidate the role of the CD in the pathogenesis of achalasia and GERD development after POEM.

A subgroup analysis that stratified patients with inspiratory augmentation loss into endoscopy-proven reflux esophagitis and non-erosive reflux disease phenotype groups did not reveal statistically significant associations (Supplementary Table), suggesting that impaired CD function may predispose patients to GERD, irrespective of the phenotype. However, because the sample size was limited, these results should be interpreted with caution.

EGJ morphology is a recognized risk factor for GERD.[17] In our cohort, type III EGJ morphology was more frequently observed in the GERD group; however, the difference between the GERD and non-GERD groups was not statistically significant, likely because of the limited sample size. EGJ pressure morphology reflects the degree of spatial coupling between the LES and CD and, thus, the capacity for inspiratory augmentation. In patients with type I morphology (complete overlap), diaphragmatic contraction effectively augments EGJ pressure; however, patients with type II morphology exhibit intermediate augmentation. Type III morphology, which is defined by separation > 2 cm between the LES and CD and considered an indicator of hiatal hernia on HRM images, disrupts LES–CD coupling and diminishes inspiratory augmentation, thus weakening the anti-reflux barrier.[7,17,18] Because inspiratory augmentation is a key protective mechanism against reflux, reduced augmentation in type III morphology has been associated with greater acid exposure and reflux burden. In our cohort, inspiratory augmentation loss was more commonly observed with type III morphology (Table 4). Therefore, our findings align with this mechanism; however, the difference was not statistically significant. Furthermore, these findings indicate that inspiratory augmentation loss before POEM may be a marker of enhanced risk rather than a predictive marker because restoration of inspiratory augmentation after POEM did not prevent GERD in our cohort.

A short intra-abdominal segment leads to reflux with small increases in intra-abdominal pressure.[19] Our findings suggested that GERD development occurs more frequently in patients with a shorter intra-abdominal LES length; however, the difference was not statistically significant (P = 0.070).

A longer gastric myotomy length has recently been reported as a risk factor for moderate to severe reflux esophagitis.[5,20] However, we found no significant difference in the gastric myotomy length between the GERD and non-GERD groups. This discrepancy may be attributed to the relatively small sample size of our study. Additionally, the gastric myotomy length in our cohort was not measured using the most objective method, such as the two-scope illumination technique, thereby potentially introducing subjectivity and measurement errors.

This study had some limitations. This was a single-center study; therefore, the generalizability of the results may be limited. Additionally, the analyses were retrospective. Eckardt scores before and after POEM were not uniformly available, thus constraining symptom-based comparisons. GERD was defined based on endoscopic esophagitis and symptom-driven PPI initiation; therefore, objective reflux test results, such as pH impedance/acid exposure times and validated GERD symptom scores, were not consistently obtained, which may have inflated the prevalence of GERD and resulted in misclassification. Finally, a markedly elevated LES tone can mask inspiratory augmentation on HRM images; therefore, reduced inspiratory augmentation before POEM may not exclusively reflect CD dysfunction.

In conclusion, loss of inspiratory augmentation before POEM was associated with GERD development after POEM and may help identify patients at high risk. However, the predictive value of inspiratory augmentation is uncertain; therefore, prospective validation is required.

SUPPLEMENTARY MATERIAL

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at http://doi.org/10.5056/jnm25120.

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