Impaired Proximal Esophageal Contractility Predicts Pharyngeal Reflux in Patients With Laryngopharyngeal Reflux Symptoms

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OBJECTIVES: The pathophysiology of laryngopharyngeal reflux (LPR) remains incompletely understood. Proximal esophageal motor dysfunction may impair bolus clearance, increasing the risk of pharyngeal refluxate exposure. We aimed to evaluate the association of proximal esophageal contractility with objective reflux metrics.

METHODS: We evaluated adults with LPR symptoms undergoing high-resolution manometry (HRM) and combined hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing at a tertiary center between March 2018 and August 2019. Routine parameters per Chicago classification were obtained on HRM. Proximal esophageal contractility was evaluated using proximal contractile integral (PCI), which quantifies contractile pressure >20 mm Hg for the region spanning the distal margin of the upper esophageal sphincter and transition zone. Univariate (Kendall correlation and Student t test) and multivariable (general linear regression and logistic regression) analyses were performed.

RESULTS: We enrolled 138 patients (66.7% women, mean age 57.1 years) in this study. Lower PCI was associated with an elevated risk of increased pharyngeal reflux (adjusted odds ratio 0.83 per 100 mm Hg-s-cm change in PCI, 95% confidence interval: 0.69–0.98), with a trend toward increased bolus exposure time and total reflux events, after multivariable adjustment. The relationship between PCI and pharyngeal reflux was strongest among participants without a primary motility disorder on HRM (adjusted odds ratio 0.63, 95% confidence interval: 0.42–0.85, P interaction = 0.04). Among continuously expressed reflux parameters, lower PCI was significantly associated with more distal acid reflux events (β = −0.0094, P = 0.03) and total reflux events (β = −0.0172, P = 0.05), after adjusting for confounders.

DISCUSSION: Reduced proximal esophageal contractility as assessed by decreased PCI on HRM independently predicted increased pharyngeal reflux in patients with LPR symptoms, particularly among those without a coexisting motility disorder.
of the distal esophagus. Peristalsis in the proximal esophagus is controlled exclusively by the central nervous system through vagal innervation (19). Aside from these functional differences, proximal esophagus motor function is the last mechanism against the escape of gastric contents past the upper esophageal sphincter (UES) and into the upper respiratory tract. The laryngopharynx lacks the effective stripping function of the esophagus and is less able to readily clear caustic materials. Thus, if reflux cannot be cleared by the upper esophagus, it may come into contact with highly sensitive laryngopharyngeal tissues for a longer period of time (20). Several small studies have identified abnormalities in proximal esophageal motor function among patients with symptoms of LPR (21,22). However, other results have been contradictory (23). Consequently, there remain few and discordant data about motility dysfunction in LPR, and its contribution to full-column esophagopharyngeal reflux (pharyngeal reflux) events is unclear.

In this study, we aimed to evaluate proximal esophageal contractility in a cohort of patients with LPR symptoms and examine its association with objective esophagopharyngeal reflux metrics.

MATERIALS AND METHODS

Study population

Adult patients with suspected LPR who were referred to a tertiary center for high-resolution manometry (HRM) and a 24-hour combined hypopharyngeal-esophageal multichannel intraluminal impedance (HEMII-pH) and dual pH testing from March 2018 to August 2019 were enrolled in this study. All patients were initially seen by an otolaryngologist with subspecialty training in laryngology. LPR was suspected by history and correlation with findings on laryngoscopic and/or stroboscopic examination, warranting referral for HEMII-pH and HRM testing. Patients with a history of esophageal or other foregut surgery, underlying pulmonary disease, sinus abnormalities, and laryngeal malignancies, were excluded. All patients completed HEMII-pH and HRM off acid-suppression medications for at least 7 days. This study was approved by the institutional review board of Mass General Brigham Healthcare, and informed consent was obtained from each subject before participation.

High-resolution manometry

Esophageal motor function was assessed with HRM. After an overnight fast, an HRM catheter (Diversatek Healthcare, Highlands Ranch, CO) consisting of 32 circumferential pressure sensors was introduced transnasally after application of topical anesthesia to the nasopharynx. The catheter was positioned so that the distal end was in the stomach and the proximal sensors were above the UES. Participants underwent a brief resting period to assess baseline esophageal parameters before performing ten 5-mL liquid swallows in the supine position.

HRM data were analyzed using the Zvu software package. Standard manometric parameters were measured and categorized in accordance with the Chicago Classification v3.0 (24). In addition, proximal esophageal motor function was evaluated using the proximal contractile integral (PCI), which quantifies contractile pressure >20 mm Hg for the region spanning the distal margin of the UES and transition zone (Figure 1a). The median PCI across all swallows was subsequently calculated for each participant. To evaluate the UES, we recorded the UES pressure, which measures the basal pressure across the UES during the resting period. The presence and size of a hiatal hernia were additionally measured.

HEMII-pH testing

Reflux burden was assessed using HEMII-pH, as described in previous publications (25). In brief, the HEMII-pH catheter contains 2 pH sensors and 8 esophageal impedance electrodes located within/above the UES and in the esophageal body. The impedance electrode pairs are divided into pharyngeal (3 and 1 cm above UES and 1 cm below UES), proximal esophageal (1, 3, and 5 cm below UES), and distal esophageal (9, 11, and 13 cm below UES) (Figure 1b). A pharyngeal reflux event is characterized by at least 50% decrease in impedance, propagating in a retrograde fashion from the distal most electrode pairs to the pharyngeal impedance electrode pairs (25) (Figure 1c).

HEMII-pH tracings were manually analyzed with the assistance of a dedicated software package (BioView Analysis, version 5.6.3.0; Sandhill Scientific, Highlands Ranch, CO). Increased reflux burden was defined as ≥4% for acid exposure time (AET), ≥1.4% for bolus exposure time (BET), and ≥73 episodes/24 hours for total reflux episodes (26). Increased pharyngeal reflux was defined as >1 pharyngeal reflux events over 24 hours on HEMII-pH, as suggested by previous normative data based on measurements among healthy individuals (27–30).

Symptom measurements

Validated symptom and health-related quality of life instruments were prospectively collected at the time of esophageal function testing, including reflux symptom index (RSI), GERD questionnaire (GERDQ), and the 12-Item Short Form Health Survey. Symptom burden was also evaluated for the dominant esophageal symptoms (heartburn, belching, regurgitation, chest pain, liquid dysphagia, and solid dysphagia) and throat symptoms (cough and wheezing) using a validated survey described in previous publications (31). Each item was rated on a 5-point Likert scale for symptom frequency (from 0 = no symptoms to 4 = multiple daily episodes) and severity (from 0 = no symptoms to 4 = very severe symptoms). Dominant symptom intensity (DSI) was obtained by multiplying the frequency and severity of the dominant symptom identified by the patient. A separate DSI was generated for esophageal symptoms and throat symptoms.

Statistical analysis

Kendall tau rank correlation was computed, and general linear regression was performed to assess the relationship between proximal esophageal motor function and reflux burden. Student t test and multivariable logistic regression were used to assess dichotomized reflux burden parameters. Multivariable regression analyses were adjusted for age, sex, body mass index (BMI), smoking status (ever smoker vs never smoker), and percentages of ineffective swallows per Chicago Classification v3.0 (distal contractile integral [DCI] < 450 mm Hg-s-cm). We next performed stratified logistic regression analyses for the relationship between proximal contractility and pharyngeal reflux according to the presence of a hiatal hernia, UES pressure, and presence of a primary motility disorder on HRM. Interaction was assessed by evaluation of the cross-product of PCI and the stratification variable using the Wald test. For these analyses, the UES pressure was dichotomized at the median value across all participants. Odds ratios are expressed per 100 mm Hg-s-cm change in PCI. Statistical analyses were performed using R 3.6.0.

RESULTS

We enrolled 138 participants, among whom 92 (66.7%) were female. The mean age was 57.1 ± 16.0 years, and the BMI was 26 (23–30)
kg/m². The most common symptoms reported were throat clearing (n = 106, 89.1%), heartburn (n = 84, 71.2%), and globus sensation (n = 83, 70.3%). The mean RSI was 18.8 (SD = 10.2), and GERDQ was 7.7 (SD = 2.4). Other detailed demographic and clinical characteristics of the study cohort are summarized in Table 1.

PCI and HEMII-pH parameters
The median PCI across all participants was 287 mm Hg-s-cm (interquartile range: 137–466). PCI was significantly correlated with DCI (r = 0.34 P < 0.001). Significant inverse correlation was found between PCI and BET (r = −0.180, P < 0.01) and total reflux episodes (r = −0.120, P = 0.04) (Table 2). There was also a trend toward increased proximal reflux with lower PCI, although statistical significance was not reached (r = −0.099, P = 0.09). On multivariable analyses, adjusting for age, sex, BMI, smoking status, and percentage of ineffective swallows, PCI remained inversely associated with distal acid reflux events (β = −0.0094, P = 0.03) and total reflux events (β = −0.0172, P = 0.05).

We next examined the association between PCI and pathologic reflux expressed as a dichotomized outcome, using

Figure 1. (a) Measurement of the PCI on HRM. (b) The HEMII-pH catheter contains 2 pH sensors located within/above the upper esophageal sphincter and in the esophageal body and 6 impedance electrodes pairs, divided into pharyngeal (3 and 1 cm above UES and 1 cm below UES), proximal esophageal (1, 3 and 5 cm below UES), and distal esophageal (9, 11, and 13 cm below UES). (c) A full-column, pharyngeal reflux event on HEMII-pH, characterized by a ≥50% decrease in impedance, propagating from the distal esophageal to the pharyngeal electrode pairs in a retrograde fashion. HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance; HRM, high-resolution manometry; PCI, proximal contractile integral; UES, upper esophageal sphincter.
thresholds established by previous normative data. On univariate analyses, PCI was significantly lower among patients with increased pharyngeal reflux (272 vs 391 mm Hg-s-cm, \( P = 0.01 \)), AET (281 vs 374 mm Hg-s-cm, \( P = 0.04 \)), BET (281 vs 410 mm Hg-s-cm, \( P < 0.01 \)), and total reflux episodes (206 vs 355 mm Hg-s-cm, \( P = 0.02 \)), compared with patients with a normal reflux burden (Figure 2). On separate multivariable logistic regression models constructed for each reflux parameter and adjusting for potential confounders, each 100 mm Hg-s-cm reduction in PCI was associated with a 17% higher risk of increased pharyngeal reflux (adjusted odds ratio [aOR] 0.83, 95% confidence interval [CI]: 0.69–0.98, \( P = 0.04 \)). There was a trend toward significance in the relationship between PCI and total reflux (aOR 0.65, 95% CI: 0.39–0.96, \( P = 0.06 \)) and increased BET (aOR 0.88, 95% CI: 0.74–1.02, \( P < 0.10 \)), but not increased AET (Table 3).

### Table 1. Baseline demographic and clinical characteristics of the study population

| Demographics | | | |
|-------------|---|---|
| Age (yr) | 63 [46–69] |
| Female sex, n (%) | 92 (66.7) |
| BMI (kg/m²) | 26 [23–30] |
| Former or current smoker (%) | 45 (32.6) |
| Current regular alcohol use (%) | 63 (47.4) |
| Symptom burden | | | |
| Reflux Severity Index score | 17 [12–25] |
| GERDQ score | 7 [6–9] |
| Dominant throat symptom index | 4 [1–12] |
| Dominant esophageal symptom index | 3 [0–12] |
| HRQOL on the SF-12 | 52 [47–56] |
| Clinical testing | | | |
| UESP (mm Hg) | 126 [72–226] |
| Hiatal hernia on HRM (%) | 23 (16.7) |
| Motility disorder on HRM (%) | 59 (43.1) |
| IEM | 40 (29.0) |
| EGJ outflow obstruction | 11 (8.0) |
| Jackhammer | 5 (3.6) |
| Absent contractility | 2 (1.4) |
| Achalasia type I | 2 (1.4) |
| Distal AET | 0.9 [0.2–2.6] |
| Distal acid reflux events | 8 [3–18] |
| Proximal AET | 0 [0–0] |
| Proximal acid reflux events | 0 [0–0] |
| BET | 1.4 [0.8–2.4] |
| Total reflux events | 34 [21–49] |
| Proximal reflux events | 14 [8–25] |
| Pharyngeal reflux events | 1 [0–3] |

The median [IQR] is presented for continuous variables.

AET, acid exposure time; BET, bolus exposure time; BMI, body mass index; EGJ, esophagogastric junction; HRM, high-resolution manometry; HRQOL, health-related quality of life; IEM, ineffective esophageal motility; IQR, interquartile range; SF-12, 12-Item Short Form Health Survey; UESP, upper esophageal sphincter pressure.

### Table 2. Correlation between PCI and reflux burden

| Reflux parameter | \( T \) | \( P \) value |
|------------------|--------|-------------|
| pH testing parameters | | |
| Distal AET | −0.059 | 0.34 |
| Distal acid reflux events | −0.089 | 0.15 |
| Proximal AET | −0.018 | 0.80 |
| Proximal acid reflux events | −0.049 | 0.49 |
| Impedance testing parameters | | |
| BET | −0.180b | <0.01a |
| Total reflux events | −0.120b | 0.04a |
| Proximal reflux events | −0.099b | 0.09b |
| Pharyngeal reflux events | −0.098 | 0.13 |

Analysis of acid reflux exposure was conducted only among patients tested off proton pump inhibitors. AET, acid exposure time; BET, bolus exposure time; PCI, proximal contractile integral.

\(^{a} P < 0.06.\)

\(^{b} P < 0.10.\)

### Esophageal dysmotility and HEMII-pH parameters

Given the identified associations between proximal esophageal function and reflux parameters, we consequently sought to examine whether these parameters differed according to distal esophageal function, as defined by the Chicago Classification v3.0. Overall, 59 patients (43.1%) were found to have a motility disorder, with ineffective esophageal motility (IEM) being the most common (n = 39, 28.3%). Participants with minor disorders (e.g., IEM) were more likely to have increased proximal reflux compared with those with disorders of esophageal peristalsis or outflow obstruction (achalasia, esophagogastric junction outflow obstruction, Jackhammer esophagus, or absent contractility) (37/39 vs 65/79, \( P < 0.05 \)). Other measures of proximal and distal exposures, both acid and nonacid, did not seem to differ by Chicago Classification groupings. In addition to esophageal body motor function, we also assessed the UES barrier activities by obtaining its basal pressure and residual pressure with swallowing. Neither UES parameter demonstrated significant associations with any of the reflux measures on HEMII-pH.

### Stratified analyses

Stratified analyses revealed that the association between PCI and increased pharyngeal reflux was most significant among participants without a coexisting motility disorder on HRM as defined by Chicago Classification v3.0 (aOR 0.63, 95% CI: 0.42–0.85, \( P < 0.03 \)) or normal manometry (37/39 vs 65/79, \( P = 0.05 \)). Other measures of proximal and distal exposures, both acid and nonacid, did not seem to differ by Chicago Classification groupings. In addition to esophageal body motor function, we also assessed the UES barrier activities by obtaining its basal pressure and residual pressure with swallowing. Neither UES parameter demonstrated significant associations with any of the reflux measures on HEMII-pH.

### Symptom assessment

There were no significant associations between PCI and measures of symptoms and severity, including RSI, GERDQ, DSI, and...
health-related quality of life on the 12-Item Short Form Health Survey ($P > 0.05$). Similarly, symptoms measured on these scales did not differ by pharyngeal reflux exposure measured on HEMII-pH ($P > 0.05$).

**DISCUSSION**

In our cohort of patients with LPR symptoms who were prospectively enrolled and systematically evaluated with HRM and HEMII-pH, we found that impaired contractility of the proximal esophagus was independently associated with increased pharyngeal reflux events. This observed risk of increased pharyngeal reflux associated with impaired proximal contractility was particularly elevated among patients without a primary esophageal motility disorder per Chicago classification on HRM. Together, our findings suggest a role for proximal esophageal contractile dysfunction in LPR which may be independent of distal esophageal motility.

Although the contribution of aberrant esophageal motor function, such as IEM and large peristaltic break, to typical GERD symptoms has been well established (9–13), less is known about the role of dysmotility in extraesophageal reflux syndromes, with previous studies reporting inconsistent results. In an early study of patients with LPR symptoms who underwent conventional esophageal manometry and pH monitoring, the presence of an esophageal motility disorder did not correlate with abnormal acid reflux (14). However, in a later study of patients with chronic cough, weak peristalsis in the distal esophagus and large peristaltic breaks on HRM were significantly associated with increased AET and decreased refluxate clearance, although the proximal esophageal and total reflux events were not different (15). Long peristaltic break was also found to correlate with cough as a presenting symptom in another study of patients undergoing both pH-impedance testing and HRM, although it was not associated with reflux burden, symptom association, or other symptom metrics (17). Notably, the presence of a long peristaltic break in this cohort of patients with cough predicted suboptimal symptom response to antireflux therapy (17), suggesting a possible protective role of intact esophageal peristalsis against extraesophageal reflux symptoms. We also previously reported that increased failed swallows in the distal esophagus independently correlated with increased RSI score among patients presenting with LPR symptoms (32). Therefore, our study contributes to the growing evidence of the possible role of esophageal dysmotility in the pathophysiology of LPR. It further adds to current literature by exploring the relationship between proximal esophageal function and pharyngeal reflux events because previous studies have largely focused on the more routinely measured distal esophageal parameters and standard GERD metrics.

A number of studies have evaluated and found increased prevalence of inappropriate or excessive relaxation of the UES among patients with LPR symptoms (18,23,33–38). The findings of this investigation suggest that, in addition to aberrant UES function, motor abnormalities of the proximal esophagus may also permit increased passage of gastric refluxate into the upper aerodigestive tract. Our findings also corroborate earlier evidence from smaller studies on proximal esophageal and UES functions in patients with laryngeal symptoms and globus sensation (21,22). Peng et al. (22) performed a small case-control study and found that the UES residual pressure was higher and the proximal esophageal contraction was lower among patients with globus sensation compared with controls. In the study by Passaretti et al.

**Table 3. Multivariate models predicting reflux exposure**

| Reflux parameter                  | aOR (95% CI) | P value |
|-----------------------------------|--------------|---------|
| AET                               | 0.89 (0.74–1.05) | 0.19 |
| BET                               | 0.88 (0.74–1.02) | <0.10 |
| Pharyngeal events                 | 0.83 (0.69–0.98) | 0.04 |
| Total reflux episodes              | 0.65 (0.39–0.96) | 0.06 |

All models were controlled for age, sex, BMI, smoking status, and percentage of ineffective swallows.

AET, acid exposure time; aOR, adjusted odds ratio; BET, bolus exposure time; BMI, body mass index; CI, confidence interval; PCI, proximal contractile integral.

*ORs are expressed per 100 mm Hg-s-cm change in PCI.
suggests an independent mechanism of pharyngeal repathophysiology of LPR. In light of these muscle interactions in the transition zone (15) may underlie the in contrast to many previous, smaller studies. The addition of These data allowed us to adjust for several potential confounders, proximally large cohort of patients with LPR symptoms who unassessed as part of the comprehensive evaluation of patients with proximal esophageal motility should be further explored and occurs in the context of preserved distal motor function. This global esophageal motor dysfunction. This was especially im-

The observed inverse correlation between PCI and pharyngeal reflux was independent of distal esophageal function. In partic-

This study has several important strengths. We leveraged data across a number of clinical and testing parameters from a rela-

development of proximal esophageal motor function is not currently incorporated into established diagnostic criteria for primary motility disorders for routine clinical care (39). Consequently, these results provide further evidence that proximal esophageal motility should be further explored and assessed as part of the comprehensive evaluation of patients with symptoms of the upper aerodigestive tract. This study has several important strengths. We leveraged data across a number of clinical and testing parameters from a relatively large cohort of patients with LPR symptoms who underw...
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.

Study Highlights

WHAT IS KNOWN

☑ The pathophysiology of laryngopharyngeal reflux remains incompletely understood.

☑ Motor dysfunction of the esophagus may impair bolus clearance, modulating the risk of pharyngeal reflux exposure.

WHAT IS NEW HERE

☑ Reduced contractility of the proximal esophagus as assessed by decreased proximal contractile integral on high-resolution manometry is independently associated with increased pharyngeal reflux.

☑ The association between proximal contractile integral and pharyngeal reflux was strongest among those with preserved distal esophageal motor function.

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