The Prevalence and Clinical Significance of Esophageal Motility Disorders in Patients Presenting With Laryngopharyngeal Reflux (LPR) Symptoms

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Accessibility
The Prevalence and Clinical Significance of Esophageal Motility Disorders in Patients Presenting with Laryngopharyngeal Reflux (LPR) Symptoms

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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

1 March 2020

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Abstract

The Prevalence and Clinical Significance of Esophageal Motility Disorders in Patients Presenting with Laryngopharyngeal Reflux (LPR) Symptoms

Daniel R. Sikavi, Jennifer X. Cai, Thomas L. Carroll, Walter W. Chan

Purpose: Esophageal motor dysfunction may underlie impaired bolus and refluxate clearance in laryngopharyngeal reflux (LPR). However, the prevalence of co-existing esophageal dysmotility and correlation with reflux parameters and symptoms in LPR is unknown.

Methods: We conducted a retrospective study of 194 consecutive patients with suspected LPR referred for high-resolution manometry (HRM) and combined hypopharyngeal-esophageal multichannel intraluminal impedance and pH testing (HEMII-pH) at a tertiary center between 3/2018 and 8/2019. Validated symptom surveys were prospectively collected at the time of testing, including Reflux Symptom Index (RSI), Gastroesophageal Reflux Disease Questionnaire (GERD-Q), and 12-item short-form health survey (SF-12). HRM findings were categorized using the Chicago Classification v3.0.

Results: Abnormal findings on HRM were identified in 43.8% of patients, of which the most common diagnosis was ineffective esophageal motility (33.0%). A disorder of esophagogastric junction (EGJ) outflow or a major disorder of peristalsis was identified in 13.4% of patients. Patients reporting esophageal symptoms upon presentation were more likely to have a primary motility disorder, and those symptoms tended to be more severe. Pharyngeal reflux exposure did not differ across HRM findings.

Conclusion: Esophageal motility disorders are prevalent among patients with LPR symptoms, including up to one in eight with either a disorder of EGJ outflow or major disorder of peristalsis. Patients with these conditions are more likely to report esophageal symptoms on presentation. The role of esophageal motor dysfunction in patients with LPR symptoms remains to be further defined.
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# Glossary of Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AET</td>
<td>Acid Exposure Time</td>
</tr>
<tr>
<td>EGJ</td>
<td>Esophagogastric Junction</td>
</tr>
<tr>
<td>GERD-Q</td>
<td>Gastroesophageal Reflux Disease Questionnaire</td>
</tr>
<tr>
<td>HEMII-pH</td>
<td>Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance and pH Testing</td>
</tr>
<tr>
<td>HRM</td>
<td>High Resolution Manometry</td>
</tr>
<tr>
<td>IEM</td>
<td>Ineffective Esophageal Motility</td>
</tr>
<tr>
<td>LES</td>
<td>Lower Esophageal Sphincter</td>
</tr>
<tr>
<td>LPR</td>
<td>Laryngopharyngeal Reflux</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>RSI</td>
<td>Reflux Severity Index</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short-Form Health Survey</td>
</tr>
<tr>
<td>UES</td>
<td>Upper Esophageal Sphincter</td>
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</table>
Scholarly Project Statement

This attached manuscript, “The Prevalence and Clinical Significance of Esophageal Motility Disorders in Patients Presenting with Laryngopharyngeal Reflux (LPR) Symptoms” aims to better characterize the pathophysiologic alterations that underlie laryngopharyngeal reflux (LPR). LPR is a complex condition in which a variety of mechanisms can produce a similar constellation of symptoms. Better understanding this disorder is particularly important in light of the limited efficacy of available therapies, which aim to suppress gastric acid production or decrease the entry of gastric refluxate into the upper airway. In order to develop more effective interventions for this highly symptomatic condition, the pathophysiology of LPR must be further elucidated.

With this aim, this project aimed to identify the co-occurrence of esophageal motility disorders among patients presenting with LPR symptoms. We concurrently assessed the correlation of dysmotility patterns with objectively measured reflux parameters and symptoms. In one of the largest series of patients with LPR symptoms systematically evaluated with high-resolution manometry and pH/impedance testing, we found a nearly 50% prevalence of esophageal motility disorders, which included a surprisingly high rate of esophagogastric junction outflow disorders or major disorders of peristalsis. We found that patients with these conditions are likely to report esophageal symptoms as a primary complaint, and symptoms tend to be more severe. The results of this project, described in the attached manuscript, will be submitted soon to a peer-reviewed journal.

This manuscript represents work carried out under the guidance of my faculty mentor, Walter W. Chan, MD. Dr. Chan and I jointly designed the project, and I principally led the project’s execution. These steps involved performing chart reviews, extracting conventional manometry and pH/impedance parameters from clinical reports, and entering survey data for all patients. In addition, under the instruction of Dr. Chan, I reviewed all of the high-resolution manometry tracings for the patients to record novel manometric parameters that characterize the motor function of the upper esophagus and which are not part of standard clinical reporting. Upon collection of the data, I worked with Dr. Chan to devise a plan for statistical analyses, the code for which I wrote independently using the R statistical package. Manuscript writing was carried out by myself and revised after review by Dr. Chan.
Appendix

The Prevalence and Clinical Significance of Esophageal Motility Disorders in Patients Presenting with Laryngopharyngeal Reflux (LPR) Symptoms

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Introduction

Laryngopharyngeal reflux (LPR) is a heterogeneous condition that is caused by the reflux of gastric contents into the larynx and pharynx. This reflux leads to laryngeal inflammation, which can manifest as chronic cough, dysphonia, and globus sensation\(^1\). There is growing evidence that both acid and non-acid reflux play a role in the development of LPR. Pepsin exposure, in particular, has been identified as a potential cause of laryngeal inflammation and extraesophageal reflux symptoms\(^2\). The diagnosis of LPR is challenging given the lack of a gold standard test, but it is most often made on the basis of both clinical criteria and the results of reflux monitoring tests such as pH and impedance studies. The latter establishes the presence of pathologic reflux events, both acid and non-acid\(^3,4\). Newer reflux testing catheters allow further delineation of reflux events that may reach the proximal esophagus and even the hypopharynx, therefore providing more specific identification of true full-column, esophago-pharyngeal reflux.

Patients with abnormal esophageal motor function may have greater difficulty clearing both acid and non-acid refluxate, which may, in turn, reach and irritate the laryngopharynx. Previous studies have found an association between esophageal hypomotility and reflux symptoms, both typical and atypical\(^5-7\). In one study of patients with LPR symptoms, the frequency of abnormal esophageal motility on esophageal manometry was 73%\(^6\). However, the precise patterns of esophageal dysmotility and correlation with patient symptoms in LPR have yet to be fully characterized. Furthermore, the relationship between dysmotility and reflux parameters in this population requires further investigation. The majority of previous studies did not utilize proximal esophageal and pharyngeal impedance testing in their evaluation in the evaluation of LPR. We have recently shown that dual pH probes without impedance testing may under diagnose LPR\(^4\).

In the present investigation, we evaluated the prevalence of co-existing esophageal dysmotility among patients with suspected LPR. We concurrently assessed the correlation of dysmotility patterns with objectively measured reflux parameters and symptoms in a population of patients presenting with LPR symptoms.
Methods

Participants
This study was approved by the institutional IRB, and informed consent was obtained from each participant prior to participation. Adult patients with suspected LPR who were referred to our center for high-resolution manometry (HRM) and combined hypopharyngeal-esophageal multichannel intraluminal impedance and pH testing (HEMII-pH) from March 2018 to August 2019 were eligible for inclusion. All patients were initially seen by an otolaryngologist with subspecialty training in laryngology and were suspected of having LPR based on history and correlation with laryngoscopic and/or stroboscopic exam findings. Patients may have had other laryngeal pathologies present, but LPR was still suspected to play a role in the presenting symptoms, warranting referral for HEMII-pH and HRM testing. Patients tested both on and off proton-pump inhibitors were included. Patients with a prior history of esophageal or other foregut surgery were excluded.

HEMII-pH Testing
Reflux exposure was assessed by HEMII-pH. All patients underwent testing after an overnight fast. The HEMII-pH detection system consists of a portable electronic data logger and transnasal catheter equipped with two pH sensors and eight esophageal impedance electrodes with locations above the upper esophageal sphincter (UES) and within the esophageal body. Impedance electrode pairs were located 2 cm apart from one another. Pharyngeal reflux was assessed at pairs starting at 3 cm and 1 cm above the UES. Proximal esophageal events were detected at pairs starting 1 cm and 3 cm below the UES. Distal reflux events were measured at pairs starting 9 cm and 11 cm below the UES. HRM was used to guide catheter placement to ensure that the proximal pH sensor was placed within the UES. Subjects were instructed to continue their normal activities, including meals, during the 24-hour study. Meal periods were documented on the portable data logger and excluded from analysis. HEMII-pH tracings were reviewed with the assistance of a dedicated software package (Bioview Analysis, version 5.6.3.0; Sandhill Scientific Inc., Highlands Ranch, CO).

High Resolution Manometry
Esophageal motor function was assessed with HRM. After an overnight fast, a HRM catheter consisting of 32 circumferential pressure and 16 circumferential impedance 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 resting esophageal function before performing ten 5-mL swallows in the supine position. Raw data from HRM was analyzed using the Zvu software package (Sandhill Scientific Inc., Highlands Ranch, CO). The Chicago Classification v3.0 was used to classify HRM findings.

**Symptom Scoring**

Validated symptom surveys were prospectively collected at the time of HEMII-pH and HRM testing. These questionnaires included the Reflux Symptom Index (RSI), Gastroesophageal Reflux Disease Questionnaire (GERD-Q), and the 12-item Short Form Health Survey (SF-12).

**Statistical Analysis**

Descriptive statistics were used to examine the demographic and clinical characteristics of the study cohort and to estimate the prevalence of co-morbid esophageal motility disorders among LPR patients. Univariate analyses were conducted to assess patient symptoms and reflux burden across HRM findings. ANOVA was used for the analysis of continuous variables, and Fisher’s exact test was used for dichotomous variables. Analysis of acid reflux burden was restricted to patients tested off PPI. Analyses were performed in R 3.6.0.
Results

194 patients met criteria for inclusion. 127 participants (65.4%) were female, and the mean age was 55.9 years (SD 15.8). Detailed demographic and clinical characteristics of the study sample are displayed in Table 1. Abnormal findings on HRM were identified in 85 (43.8%) participants (95% CI: 36.8%-50.8%). The most common diagnosis was ineffective esophageal motility (33.0%). A disorder of esophagogastric junction (EGJ) outflow or a major disorder of peristalsis was diagnosed in 26 (13.4%) participants (Table 2).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>55.9 ± 15.8</td>
</tr>
<tr>
<td>Female, n (%).</td>
<td>127 (65.4%)</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27.9 ± 6.5</td>
</tr>
<tr>
<td>Former or current smoker, n (%)</td>
<td>59 (30.4%)</td>
</tr>
<tr>
<td>Current alcohol use, n (%)</td>
<td>89 (47.1%)</td>
</tr>
<tr>
<td>Test performed off PPI, n (%)</td>
<td>170 (90.9%)</td>
</tr>
<tr>
<td>Reflux Severity Index score (mean ± SD)</td>
<td>17.9 ± 10.2</td>
</tr>
</tbody>
</table>

Table 2. Motility disorders on HRM

<table>
<thead>
<tr>
<th>HRM Diagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I Achalasia</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>EGJ Outflow Obstruction</td>
<td>17 (8.8%)</td>
</tr>
<tr>
<td>Jackhammer Esophagus</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Absent Contractility</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Ineffective Esophageal Motility</td>
<td>64 (33.0%)</td>
</tr>
</tbody>
</table>

Note. Esophagogastric Junction (EGJ)
Includes overlapping diagnoses

When analyzing reflux exposure across HRM findings, we found significantly increased distal acid exposure time (AET) among patients with hypercontractile motility disorders (i.e., Jackhammer esophagus, distal esophageal spasm) compared to patients with normal HRM (6.5% v. 2.0%, p<0.05). There were no significant differences in pharyngeal or proximal reflux burden, either acid exposure or bolus exposure on impedance, across HRM findings (Table 3).
Table 3. Reflux burden across HRM findings

<table>
<thead>
<tr>
<th>Reflux Parameter</th>
<th>Mean Value among Patients with</th>
<th></th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal HRM</td>
<td>Hypocontractile Disorders(^1)</td>
<td>Hypercontractile Disorders(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngeal Reflux Events(^3)</td>
<td>2.84</td>
<td>2.22</td>
<td>5.20</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Proximal Reflux Events(^3)</td>
<td>0.13</td>
<td>0.35</td>
<td>0.06</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Total Reflux Events(^3)</td>
<td>0.13</td>
<td>0.35</td>
<td>0.06</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Distal Acid Exposure Time(^4)</td>
<td>1.96</td>
<td>2.66</td>
<td>6.47</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Ineffective esophageal motility, achalasia, absent contractility
\(^2\) Jackhammer esophagus, diffuse esophageal spasm
\(^3\) Expressed as events per 24 hours
\(^4\) Expressed as %

Reporting any esophageal symptom (e.g., heartburn, regurgitation, dysphagia) as part of the primary complaint on presentation was associated with greater odds of having abnormal HRM compared to those with throat symptoms (e.g., cough, wheeze) alone (OR 2.42, p=0.03) (Figure 1). Additionally, patients with any abnormal HRM finding reported higher scores on the esophageal symptom subscore of the RSI, compared to those with normal HRM (4.1 v. 3.1, p=0.02, maximum score = 10). There were no differences in scores on the RSI overall or the throat symptom subscore of the RSI across HRM findings (Table 4). The presence and specific type of motility disorder were not associated with symptom severity as measured on the GERD-Q or health-related quality of life on the SF-12.

![Figure 1. Proportion of patients with abnormal findings on HRM by primary complaint](image_url)
Table 4. Symptom scores across HRM findings

<table>
<thead>
<tr>
<th>Symptom Scale</th>
<th>Mean Score among Patients with Normal HRM</th>
<th>Mean Score among Patients with Abnormal HRM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux Severity Index (RSI)</td>
<td>17.0</td>
<td>19.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Esophageal Symptom Subscore</td>
<td>3.1</td>
<td>4.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Throat Symptom Subscore</td>
<td>17.0</td>
<td>17.5</td>
<td>0.71</td>
</tr>
<tr>
<td>GERD-Q</td>
<td>7.8</td>
<td>7.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Health-Related Quality of Life (SF-12)</td>
<td>48.9</td>
<td>49.4</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Discussion

Our results indicate that esophageal dysmotility is prevalent among patients with suspected LPR. Nearly half of patients evaluated were found to have abnormal HRM testing, with approximate one in eight patients overall found to have a disorder of EGJ outflow or a major disorder of peristalsis. Our results corroborate older studies that have similarly shown a high prevalence of HRM abnormalities among patients with extraesophageal reflux symptoms, ranging from 70-80%\(^6,13\). It is important to note, however, that these comparatively higher values were based on non-standardized HRM criteria. Similar to these prior studies evaluating patients with LPR symptoms, ineffective esophageal motility (IEM) was the most common finding. Interestingly, we found a particularly high rate of disorders of EGJ outflow and major disorders of peristalsis. Given that these patients presented for evaluation of respiratory and throat symptoms, this finding further underscores the heterogeneous presentation of esophageal motility disorders.

Esophageal dysmotility may play an important and under-recognized role in the pathogenesis of LPR. Impaired esophageal motor function may contribute to decreased bolus clearance, leading to irritation of laryngopharyngeal tissues\(^14,15\). In addition, it is possible that there might be receptor hypersensitivity in the proximal esophagus that occurs in the context of aberrant motility and heightened luminal pressures due to bolus retention. Studies have demonstrated heightened cough responses to chemical irritants among patients with GERD compared to healthy controls\(^16,17\). There is also evidence of increased sensory responses to esophageal distention among patients with globus sensation\(^18\). Failure to address abnormal esophageal motor function may explain the limited response of LPR patients to acid suppression and anti-reflux surgery\(^19-23\). New prokinetic agents have been studied in the management of LPR. However, a recent systematic review found inconclusive evidence for the use of the agents investigated\(^24\). Future therapies that can better restore esophageal motor function may be beneficial in the treatment of LPR.

In this study, abnormal HRM testing was predicted by the presence and severity of esophageal symptoms at the time of LPR evaluation. Given the high overall prevalence of esophageal dysmotility in this population, we favor routine HRM testing in all patients presenting with refractory LPR symptoms. Nonetheless, endorsement of any esophageal symptom should indicate a higher index of suspicion of an underlying motility disorder.
Interestingly, reflux exposure, both acid exposure on pH testing and bolus exposure on impedance, were relatively comparable across HRM findings. While it is possible that esophageal dysmotility contributes to LPR symptoms through increased reflux exposure, assessment on HEMII-pH testing may have been relatively insensitive to fully capture bolus events in the esophagus. In particular, analysis of pharyngeal events is particularly challenging with high rates of inter-observer concordance of findings. Furthermore, there is likely a dynamic interplay between numerous factors, both intrinsic reflux and environmental exposures, that contribute to LPR symptoms. Patients may also have variable rates of tolerance to reflux events. As a result, it may be difficult to isolate the effect of a single physiologic parameter across all patients.

The present study has a few important limitations. Due to the cross sectional nature of our design, causal relationships and temporal changes in symptoms and reflux parameters could not be assessed. The study population was drawn from a tertiary referral center. Consequently, results from this study may not be generalizable to other populations, particularly those with less severe symptoms who present in the primary care setting. Nonetheless, symptom burden as assessed by the validated Reflux Symptom Index was comparable to that of similar studies evaluating patients with pH-monitoring confirmed LPR.
Conclusion

In one of the largest series of patients with LPR symptoms systematically evaluated with HRM and HEMII-pH, we report a nearly 50% prevalence of esophageal motility disorders. In particular, up to one in eight patients were found to have either a disorder of EGJ outflow or a major disorder of peristalsis. Patients with these conditions are likely to report esophageal symptoms as a primary complaint, and symptoms tend to be more severe. HRM findings did not correlate with typical reflux parameters. Further work is needed to better understand the role of esophageal motor dysfunction in patients with LPR.
References


