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Effects of Proton Pump Inhibitor Therapy for Laryngopharyngeal Reflux on Posttreatment Symptoms and Hypopharyngeal pH

Jonathan Waxman[1,2], Sreeya Yalamanchali, MD[2], Elizabeth Shay Valle[1,2], Thomas Pott, MD[2], and Michael Friedman, MD[2,3]

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Abstract

Objective. To determine the effect of twice-daily proton pump inhibitor (PPI) treatment on the relationship between laryngopharyngeal pH environment and symptoms in patients with laryngopharyngeal reflux (LPR).

Study Design and Setting. Retrospective analysis of records from consecutive patients seen at a single clinical site between 2009 and 2012.

Subjects and Methods. Forty-three records of patients diagnosed with LPR who underwent pre- and posttreatment pH studies were included. Prior to treatment, all had a Reflux Symptom Index (RSI) $>$ 13 and an abnormal pH study. Patients were treated for $\geq$ 4 weeks with twice-daily PPIs. Following treatment, patients completed a second RSI and pH study.

Results. Most patients (67.4%) had symptom normalization; however, most patients (60.5%) did not have pH normalization. For all patients whose symptoms did not normalize, pH scores also did not normalize; 32.6% of patients showed no subjective or objective treatment response. For individuals whose symptoms normalized but whose pH scores did not normalize, there was a significant decrease in upright pH score. For the entire group, pretreatment symptom and upright pH scores were strongly positively correlated. Improvements in symptom and upright pH scores following treatment were moderately positively correlated.

Conclusion. Laryngopharyngeal pH failed to normalize for most individuals after PPI treatment; only pH improvement was necessary for symptom normalization. Many patients had no treatment response. Laryngopharyngeal reflux patients may make up a heterogeneous group, and PPI responsivity may help explain conflicting results from previous studies. Posttreatment pH monitoring is recommended in studies investigating the efficacy of PPI therapy for LPR.

Keywords

laryngopharyngeal reflux, LPR symptoms, pH monitoring, pharyngeal pH, Reflux Symptom Index

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Introduction

Laryngopharyngeal reflux (LPR) is a commonly occurring disorder that can present with a diverse set of nonspecific symptoms including chronic cough, throat clearing, hoarseness, sore throat, dysphagia, globus sensation, and postnasal drip.[1] Laryngopharyngeal reflux is highly prevalent, affecting up to 10% of patients with otolaryngological complaints.[2] Although the precise pathophysiological mechanisms that underlie LPR remain incompletely known and somewhat controversial, associations have been observed between LPR and laryngeal cancer,[3] subglottic stenosis,[4] chronic pharyngitis,[5] chronic obstructive pulmonary disease,[6] asthma,[7] and obstructive sleep apnea.[8]

Laryngopharyngeal reflux and its symptoms are often presumed to result from the reflux of acidic gastric contents beyond the upper esophageal sphincter into the laryngopharynx. This is a reasonable hypothesis given that, unlike the esophagus, which can tolerate up to 50 daily acid reflux episodes, laryngeal mucosa is poorly equipped to withstand

[1]College of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA
[2]ChicagoENT, Advanced Center for Specialty. Care, Advocate Illinois Masonic Medical Center, Chicago, Illinois, USA
[3]Rush University Medical Center, Chicago, Illinois, USA

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Corresponding Author:
Michael Friedman, MD, ChicagoENT, 30 North Michigan Avenue, Suite 1107, Chicago, IL 60602, USA.
Email: mfriedman@chicagoent.com

acidic refluxate.[9,10] As few as 3 reflux episodes can cause severe laryngeal inflammation and injury.[9] Other laryngeal mucosal irritants, such as pepsin and small intestinal bile acids, have been identified, although injury by these substances evidently requires an acidic environment.[11,12] Consequently, standard therapy for LPR is twice-daily proton-pump inhibitors (PPIs). However, for reasons that have yet to be fully elucidated, treatment with a PPI fails to alleviate the symptoms of LPR for many individuals. Moreover, there is considerable disagreement among studies aimed at assessing the effect of PPIs on LPR,[13,14] and meta-analyses have concluded that PPIs are no more beneficial than placebo for treating LPR.[15-18]

Diagnosis of LPR is typically made using a combination of clinical assessment and direct observation of mucosal injury and inflammation. The definitive confirmatory test for LPR is 24-hour ambulatory pH monitoring. However, despite repeated observations that many patients fail to respond to PPI therapy, most studies fail to measure or report changes in hypopharyngeal pH following PPI treatment. Consequently, there are few published data that correlate changes in pH to changes in symptomatology, particularly using recently developed pH measurement devices. Without these data, it is difficult to interpret the results of conflicting studies investigating the efficacy of PPI therapy for LPR in what may be a heterogeneous patient population with varying PPI responsivity. Moreover, the existing literature has not clearly established whether PPI therapy normalizes pH in the hypopharynx and if normalization correlates with clinical improvement. Hence, the objectives of this study were to compare the symptomatic improvement between patients whose laryngeal pH environment did and did not normalize, and characterize different response groups.

Materials and Methods

Patient Characteristics and Inclusion/Exclusion Criteria

Approval for this study was obtained from the Western Institutional Review Board (Puyallup, Washington). This study was conducted as a retrospective analysis of consecutive medical records extracted from a database consisting of patients who were seen at a single clinical site (ChicagoENT, Chicago, Illinois, USA) between 2009 and 2012. All patients seen at this site and suspected of having LPR initially were given 2 options, namely, to start empiric PPI treatment or undergo pH testing. Patients had the right to choose 1 or both options at any time. After starting PPI treatment, patients were evaluated on a monthly basis to assess medication adherence and response to treatment. In addition, they were given the option to be retested at least 1 month later if no response was observed. Patients who demonstrated a response were also given the option to be retested to determine if the PPI dosage could be reduced or eliminated. Records were included for patients with suspected LPR who (1) completed a Reflux Symptom Index (RSI), (2) underwent 24-hour pH testing with a Restech Dx-pH probe, (3) were prescribed 40 mg of omeprazole or pantoprazole twice daily for at least 4 weeks, (4) completed a posttreatment RSI, and (5) underwent a second pH study. The posttreatment RSI questionnaires and pH studies were completed on the same day or within several days of one another. Patients who did not meet all of the above inclusion criteria were excluded from the study.

Reflux Symptom Index

The RSI is a validated self-administered questionnaire used to assess the severity of symptoms thought to be related to LPR.[19] It consists of 9 questions rated on a 5-point Likert-type scale, whose ratings are combined to produce a total RSI score ranging from 0 (asymptomatic) to 45. Based on normative data, an RSI score greater than 13 is considered to be clinically significant and highly suggestive of LPR.

Restech Dx-pH Probe

The Restech Dx-pH probe (model Dx-201 Dx-pH probe; Restech Respiratory Technology Corporation, San Diego, California, USA) is a wireless probe that, unlike standard dual pH probes, employs a sensor that is able to measure pH in either liquid or aerosolized droplets in the posterior oropharynx.[20] This is desirable for diagnosing LPR since reflux episodes may often take the form of aerosolized gastric contents.[21] In this way, the device has been shown to reliably detect supraesophageal reflux events[22] with a high diagnostic specificity and reasonable sensitivity.[23] For each diagnostic study, pH scores were calculated as described below using the Dx-pH DataView Lite software.

RYAN Score

The RYAN score is a composite pH score based on (1) the number of episodes of pH falling below an established pH threshold, (2) the duration of the longest episode during which pH remained below the threshold, and (3) the percentage of total time spent below the threshold. The thresholds (5.5 for upright and 5.0 for supine positions) were experimentally determined to be values for which true reflux episodes were maximized and system noise was minimized.[24] At these pH thresholds, the 95th percentile values for RYAN scores were 9.4 for the upright position and 6.8 for the supine position. RYAN scores greater than these values are strongly suggestive of significant LPR.

Statistical Analysis

Records were partitioned into 4 subgroups depending on whether the associated RSI and upright and supine RYAN scores normalized after PPI treatment. For the entire group and each subgroup, means and standard deviations were calculated for age, body mass index (BMI), pre- and posttreatment variables (RSI, upright and supine RYAN scores), the duration in days between pH studies, and differences between pre- and posttreatment variables.

Statistical analysis was performed using SigmaStat version 3.2 (Systat Software, San Jose, California, USA), and a

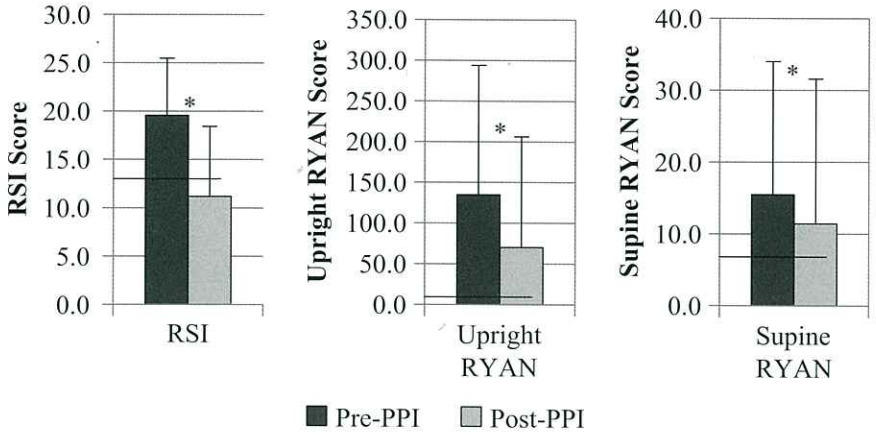

Figure 1. Pretreatment and posttreatment Reflux Symptom Index, upright RYAN, and supine RYAN. Mean ± SD values are plotted for the entire group. Dashed lines represent normalization thresholds. All 3 variables significantly decreased following proton pump inhibitor treatment ($P < .001$).

Table 1. Frequencies of Normalization of Reflux Symptom Index and Both Upright and Supine RYAN Scores following Proton Pump Inhibitor Treatment.

	Reflux Symptom Index	
RYAN Score	Normalized	Not Normalized
Normalized	17	0
Not Normalized	12	14

value of $P < .05$ was considered statistically significant. Comparisons of demographic, pretreatment, and posttreatment variables between subgroups were performed using a 1-way analysis of variance (ANOVA) or Kruskal-Wallis 1-way ANOVA on ranks (for data that failed normality or equivalence of variance tests). Post-hoc pairwise testing was performed using Tukey or Dunn tests. Chi-square tests were used to compare the frequency distributions of categorical variables. For the entire group and each subgroup, comparisons between pre- and posttreatment variables were performed using paired t tests or Wilcoxon signed rank tests (for data that failed normality tests). Finally, Pearson correlation coefficients were calculated between pairs of variables (age, BMI, pre- and posttreatment variables, and the difference between pre- and posttreatment variables).

Results

Entire Group

Forty-three records of 29 women and 14 men were included. The average ± SD age of 53.9 ± 16.8 years and the average ± SD BMI of 30.3 ± 6.8 kg/m^2 were included. The average ± SD duration of PPI treatment was 113.0 ± 89.4 days. As shown in **Figure 1**, following PPI treatment, there was a significant decrease in the RSI score, upright RYAN score, and supine RYAN score ($P < .001$ for all tests).

Subgroups

The frequencies of RSI and RYAN score normalization are shown in **Table 1**. Following PPI treatment, the RSI score normalized for 29 of the 43 (67.4%) patients. However, both upright and supine RYAN scores did not normalize for 26 (60.5%) patients. For 17 (39.5%) individuals, the RSI score and both RYAN scores normalized. We will refer to this subgroup as *Responders*. There were 12 (27.9%) patients whose RSI normalized but did not have normalization of both RYAN scores. We will call this subgroup *Partial Responders*. For all 14 (32.6%) remaining patients whose RSI did not normalize, both RYAN scores also did not normalize. This subgroup will be called *Nonresponders*. There were no patients whose RYAN scores normalized without normalization of the RSI score. Therefore, statistical analyses included 3 subgroups: Nonresponders, Partial Responders, and Responders.

The frequencies of men and women and the average ± SD values for age, BMI, treatment duration, pretreatment RSI, pretreatment upright RYAN score, and pretreatment supine RYAN score are reported for each of the 3 subgroups in **Table 2**. One-way ANOVA or Kruskal-Wallis 1-way ANOVA on ranks showed no significant differences between the groups for any of these variables.

The results for the RSI score are shown in **Figures 2A** and **2D**. Following PPI treatment, the RSI significantly decreased in the Partial Responder and Responder subgroups. This was expected, since the 2 groups were defined by RSI normalization. For the Nonresponder subgroup, the RSI score did not significantly change following treatment. Analyses of variance and post-hoc tests showed that the posttreatment RSI score for the Partial Responder and Responder subgroups was significantly lower than for the Nonresponder group ($P < .001$). However, the posttreatment RSI did not significantly differ between the Partial Responder and Responder groups. Moreover, as plotted in **Figure 2D**, the change in RSI following treatment for the Responders and the Partial Responders was significantly greater than that of the Nonresponders, but

Table 2. Demographic and Pretreatment Characteristics of the 3 Patient Subgroups.[a]

	Nonresponders (N = 14)	Partial Responders (N = 12)	Responders (N = 17)
Age, y	58.1 ± 13.8	51.8 ± 20.3	51.9 ± 17.2
Body mass index, kg/m^2	31.4 ± 6.5	32.2 ± 7.0	28.3 ± 6.7
Sex	10 W, 4 M	9 W, 3 M	10 W, 7 M
Pretreatment RSI	20.6 ± 5.6	21.2 ± 7.0	17.6 ± 5.1
Pretreatment upright RYAN	181.89 ± 245.89	162.03 ± 91.71	76.73 ± 73.99
Pretreatment supine RYAN	24.04 ± 24.87	12.51 ± 13.07	10.57 ± 13.47
Treatment duration, d	100.9 ± 64.4	93.5 ± 103.8	125.3 ± 84.0

Abbreviations: M, men; RSI, Reflux Symptom Index; W, women.
[a]No significant differences were found between the groups for any variable.

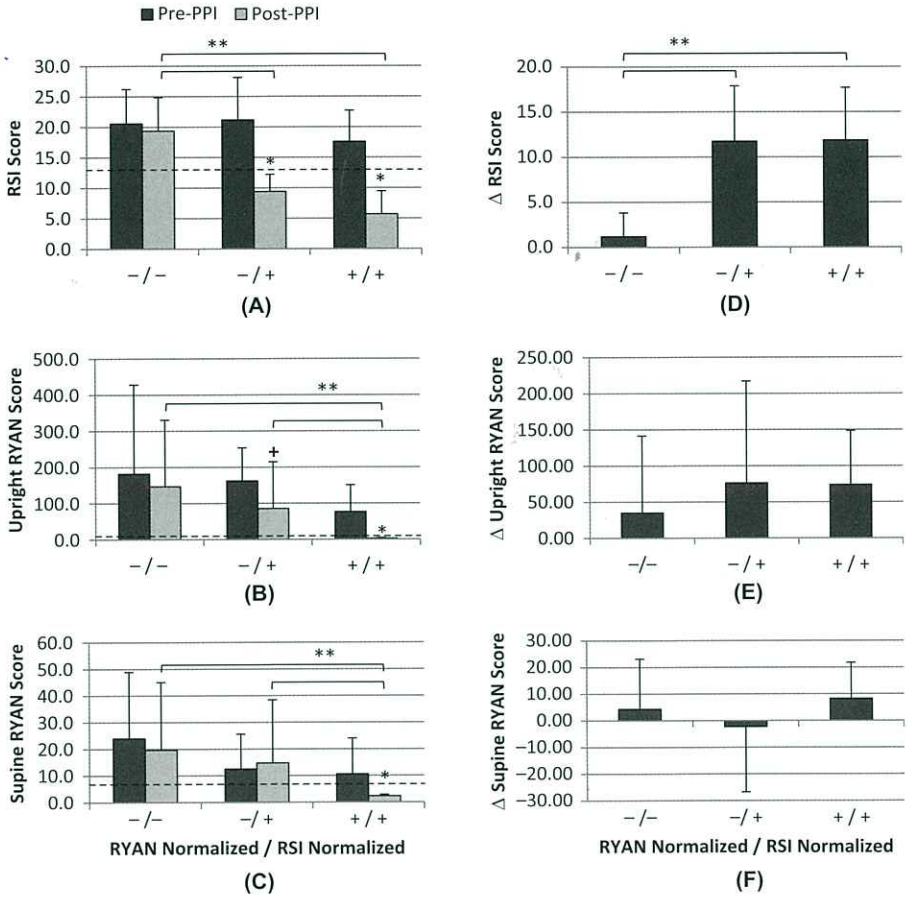

Figure 2. Mean ± SD values are plotted for nonresponders (-/-), partial responders (-/+), and responders (+/+). Dashed lines represent normalization thresholds. Significant differences are marked with single stars ($P < .001$), plus signs ($P = .042$), and double stars ($P < .05$). (A) RSI score for the three groups; (B) Upright RYAN score for the three groups; (C) Supine RYAN score for the three groups; (D) Change in RSI for the three groups; (E) Change in Upright RYAN for the three groups; (F) Change in Supine RYAN for the three groups. PPI, proton pump inhibitor; RSI, Reflux Symptom Index.

there was no difference in change between the Partial Responders and Responders.

The results for the upright RYAN score are shown in **Figures 2B** and **2E**. The upright RYAN score significantly decreased for the Responder ($P < .001$) and Partial Responder ($P = .042$) subgroups, but not for the Nonresponder subgroup. However, whereas the posttreatment upright RYAN score for the Responder group was significantly lower than the Nonresponder and Partial Responder groups ($P < .05$), the posttreatment upright RYAN score for the Partial Responders was not significantly lower than the Nonresponders. No significant results were found for the differences between pre- and posttreatment upright RYAN scores for any of the 3 patient groups.

Table 3. Correlations between Pairs of Variables for the Entire Patient Group.

		Pre–Post Difference		Pretreatment					
All Patients (N = 43)		Upright RYAN	Supine RYAN	RSI	Upright RYAN	Supine RYAN	Age	BMI	Duration
Pre–Post Difference	RSI	$r = 0.311^a$	—	$r = 0.395^b$	—	—	—	—	—
	Upright RYAN		—	$r = 0.418^b$	$r = 0.541^c$	—	$r = 0.336^a$	—	—
	Supine RYAN			—	—	$r = 0.418^c$	—	—	—
Pretreatment	RSI				$r = 0.539^c$	—	—	—	—
	Upright RYAN					—	—	—	—
	Supine RYAN						—	—	—

Abbreviations: BMI, body mass index; RSI, Reflux Symptom Index.
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.

Table 4. Correlations between Pairs of Pretreatment and Demographic Variables for the 3 Patient Subgroups.

			Pretreatment				
			Upright RYAN	Supine RYAN	Age	BMI	Duration
Pretreatment	RSI	Nonresponders	$r = 0.673^a$	—	—	—	—
		Partial Responders	—	—	—	—	—
		Responders	$r = 0.612^a$	—	$r = 0.657^a$	—	—
	Upright RYAN	Nonresponders		—	—	—	—
		Partial Responders		—	—	—	—
		Responders		—	$r = 0.489^b$	—	$r = 0.488^b$
	Supine RYAN	Nonresponders			—	—	—
		Partial Responders			—	—	—
		Responders			—	—	—

Abbreviations: BMI, body mass index; RSI, Reflux Symptom Index.
[a]$P < .01$.
[b]$P < .05$.

Finally, the results for the supine RYAN score are shown in **Figure 2C**. The supine RYAN score significantly decreased only for the Responder group ($P < .001$). The Responder posttreatment supine RYAN score was significantly lower than both the Nonresponder and Partial Responder posttreatment supine RYAN scores ($P < .05$). However, the posttreatment supine RYAN score for the Partial Responders was not significantly different from that of the Nonresponders. There were no significant differences between any of the groups for change in supine RYAN score.

Correlations

Correlations between pairs of variables for the entire group are reported in **Table 3**. For the entire group, the change in RSI score was moderately positively correlated with the change in upright RYAN score and the pretreatment RSI score ($r = 0.311$, $P < .05$ and $r = 0.395$, $P < .01$, respectively). The change in upright RYAN score was moderately to strongly positively correlated with the pretreatment RSI score ($r = 0.418$, $P < .01$), the pretreatment upright RYAN score ($r = 0.541$, $P < .001$), and age ($r = 0.336$, $P < .05$). The change in supine RYAN score was strongly positively correlated with the pretreatment supine RYAN score ($r = 0.418$, $P < .01$), and the pretreatment RSI score was strongly positively correlated with the pretreatment upright RYAN score ($r = 0.539$, $P < .001$).

Correlations between pairs of variables are shown for the patient subgroups in **Table 4**. We did not include the changes in variables because the RSI and RYAN score thresholds used to define the subgroups would bias the correlation calculations. For the Nonresponder subgroup, the pretreatment RSI score was strongly positively correlated with the pretreatment upright RYAN score ($r = 0.673$, $P < .01$). For the Responders, the pretreatment RSI score was strongly correlated with the pretreatment upright RYAN score ($r = 0.612$, $P < .01$) and age ($r = 0.657$, $P < .01$). The pretreatment upright RYAN score was strongly positively correlated with age ($r = 0.489$, $P < .05$) and treatment duration ($r = 0.488$, $P < .05$). No significant correlations were found for the Partial Responder group.

Table 5. Results from Studies, Including This One, That Report Improvement in Symptoms Related to pH Changes Following Proton Pump Inhibitor Treatment.

	pH Normalized		pH Not Normalized	
Study	Symptoms Improved	Symptoms Not Improved	Symptoms Improved	Symptoms Not Improved
Reichel et al[27] (N = 49)	44.4%	3.7%	29.6%	22.2%
Karoui et al[28] (N = 33)	45.5%	21.2%	6.1%	27.3%
Waxman et al (N = 43)	39.5%	0%	27.9%	32.6%

Discussion

Laryngopharyngeal reflux is highly prevalent and associated with numerous otolaryngologic complaints and serious potential sequelae. It is therefore important to adequately treat patients diagnosed with this disorder. Current treatment guidelines advocate twice daily PPIs for the treatment of LPR; however, evidence from the literature regarding PPI efficacy is mixed and there are few available data correlating improvements in hypopharyngeal pH with improvements in symptomatology following PPI therapy. The purpose of this study was to clarify the relationship between changes in hypopharyngeal pH and symptom severity in patients with pH study confirmed LPR. A secondary aim was to assess PPI responsivity and characterize different treatment response groups.

Our data showed that most patients in our cohort had symptomatic improvement that was strongly correlated with a reduction in laryngopharyngeal acidic environment, although only 39.5% of patients had normalization of both RYAN scores, which we considered as indicating complete pH normalization. Of the patients whose RYAN scores did not normalize, symptoms significantly improved for 46.2% following PPI therapy. These data suggest that only significant improvement, rather than normalization, of the upright RYAN score was necessary for symptom normalization. Moreover, we observed no difference in the magnitude of symptoms improvement in response to PPI treatment between the Partial Responder and Responder subgroups. It is important that we found that a large group of individuals demonstrated neither subjective nor objective responses to PPI therapy. That is, these individuals continued to report symptoms and demonstrate abnormal pH study findings despite maximum dosage PPI therapy.

Due to the retrospective design of this study, adherence to medication was self-reported and the duration between pH studies was not well controlled. It is therefore possible that our findings of a Nonresponder subgroup could be explained by poor adherence or too short a treatment duration. However, we did not observe any significant differences in treatment duration between the 3 subgroups. Moreover, the subgroup frequencies remained unchanged when only individuals with treatment durations of at least 8 weeks were included (results not shown). Nevertheless, we cannot rule out the possibility that the Nonresponder subgroup comprised individuals who were physiologically resistant to PPI therapy. Proton pump inhibitor resistance in LPR patients has been previously investigated in a retrospective study by Amin et al[25], who reported a failure rate of 40% among LPR patients on the same PPI dosage as patients in this study. This is very close to the failure rate we observed in our study. Surprisingly few studies investigating the efficacy of PPI treatment for LPR report objective posttreatment pH assessment. Of those studies that do, most fail to report changes in symptomatic improvement in relation to changes in laryngopharyngeal pH scores. Without both subjective and objective assessment of PPI efficacy, it is difficult to interpret conflicting results of different studies. The incidence of persistently abnormal pH environment in the hypopharynx has been poorly studied. Thirty-two studies were reviewed on the efficacy of PPI therapy comprising results of 1770 patients. Only 4 of these studies had limited data on posttreatment pH. Two had no data on pH of responders and limited data on pH environment of nonresponders.[26,27] The remaining 2 studies did report data on both responder and nonresponders.[28,29] **Table 5** summarizes these results as well as the results of our study. Similar to our results, Reichel et al[28] found that more than 50% of patients did not have a normal pH environment following PPI treatment. A study by Karoui et al[29] reported a pH normalization failure rate of only 33.4%. Although lower than the other studies, this study confirms a significant failure rate after PPI therapy. Symptom assessments in both studies were not based on RSI but used nonvalidated symptom questionnaires, making comparison of symptom response difficult. A study by Charbel et al[30] specifically assessed the role of pH monitoring in patients on PPI therapy who continued to report extraesophageal symptoms commonly associated with LPR. They also demonstrated that a significant number of PPI nonresponders had abnormal pH studies.

Unlike the studies mentioned above, we also measured correlations between demographic, pretreatment, and posttreatment variables. For the entire group of patients, moderate to strong correlations were observed between pretreatment values and improvements in RSI and upright RYAN scores, suggesting that PPI treatment was more effective for individuals with worse disease. Positive correlations between improvements in RSI, upright RYAN score, and supine RYAN score and pretreatment RSI, upright

RYAN score, and supine RYAN score, respectively, suggest that greater improvement following PPI treatment might be expected from patients with more severe LPR. It is interesting that we also found a significant positive correlation between upright RYAN score and age. As might be expected, we found that for the Responder subgroup, pretreatment RSI was strongly positively correlated with pretreatment upright RYAN score. It is surprising that this correlation was not significant for the Partial Responder subgroup but was significant for the Nonresponder subgroup. It is unclear why the Partial Responder subgroup did not demonstrate this relationship. It is possible that the correlation in Nonresponders might support an acid reflux etiology of their symptoms, despite no response to PPIs. However, it is important to recognize the exploratory nature of these findings, particularly because of the retrospective study design and relatively small sample sizes.

Conclusion

Our results suggest that LPR patients make up a heterogeneous group with respect to PPI responsivity. In particular, we observed 3 groups of individuals with different responses to treatment. In addition, our results show that symptom normalization may be achieved by a significant improvement, rather than complete normalization, of upright pH scores. Finally, we observed a large group of patients who failed to demonstrate any objective or subjective response to PPI therapy. Additional prospective studies are required to more carefully characterize subgroups of LPR patients who fail PPI therapy and assess additional treatment options for patients with persistent evidence of an acidic hypopharyngeal environment. We recommend that future studies employ post-treatment pH assessment and report correlations to objective and subjective measurements of LPR signs and symptoms.

Author Contributions

Jonathan Waxman, acquisition of data, analysis and interpretation of data, drafting and revising for critically important intellectual content, final approval of version to be published, and presentation at the annual academy meeting; **Sreeya Yalamanchali**, acquisition of data, analysis and interpretation of data, drafting and revising for critically important intellectual content, and final approval of version to be published; **Elizabeth Shay Valle**, acquisition of data, analysis and interpretation of data, drafting and revising for critically important intellectual content, and final approval of version to be published; **Thomas Pott**, acquisition of data, analysis and interpretation of data, drafting and revising for critically important intellectual content, and final approval of version to be published; **Michael Friedman**, study design, concept, and conduct, main investigator who placed the pH probes, statistical analysis, drafting/revision, and final approval of the version to be published.

Disclosures

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