



Published in final edited form as:

Am J Gastroenterol. 2016 November ; 111(11): 1517–1524. doi:10.1038/ajg.2016.145.

Oropharyngeal pH Testing Does Not Predict Response to Proton-Pump Inhibitor Therapy in Patients with Laryngeal Symptoms

Rena Yadlapati¹, John E. Pandolfino¹, Alcina K. Lidder², Nadine Shabeeb³, Diana-Marie Jaiyeola¹, Christopher Adkins¹, Neelima Agrawal¹, Andrew Cooper¹, Caroline P.E. Price⁵, Jody D. Ciolino¹, Andrew J. Gawron⁴, Stephanie S. Smith⁵, Michiel Bove⁵, and Bruce K. Tan⁵

¹Division of Gastroenterology and Hepatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

²University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY, USA

³University of Indiana School of Medicine, Indianapolis, IN, USA

⁴Division of Gastroenterology, University of Utah, Salt Lake City, UT, USA

⁵Division of Otolaryngology, Feinberg School of Medicine, Northwestern University, Chicago IL, USA

Corresponding Author: Rena Yadlapati, MD, Division of Gastroenterology, Northwestern University, 676 North St. Clair St. Suite 1400, Chicago, IL 60611, Office: (312) 695-4065, Fax: (312) 695-3999, rena.yadlapati@northwestern.edu.

Disclosures/Conflicts of Interest: The authors do not have any disclosures or potential conflicts of interest

Author Contributions:

Rena Yadlapati: Study oversight, study concept & design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

John E. Pandolfino: Study concept & design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Alcina K. Lidder: Study concept & design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Nadine Shabeeb: Study concept & design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Diana-Marie Jaiyeola: Study concept & design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Christopher Adkins: Study concept & design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Neelima Agrawal: Study concept & design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Andrew Cooper: Analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Caroline PE Price: Study concept & design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Jody D. Ciolino: Analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Andrew J. Gawron: Study concept & design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Stephanie S. Smith: Acquisition of data; critical revision of the manuscript for important intellectual content

Michiel Bove: Acquisition of data; critical revision of the manuscript for important intellectual content

Bruce K. Tan: Study concept & design; acquisition of data; drafting of manuscript; critical revision of the manuscript for important intellectual content

Abstract

Introduction—Predicting response to proton-pump inhibitor (PPI) therapy in patients with laryngeal symptoms is challenging. The Restech Dx-pH probe is a transnasal catheter that measures oropharyngeal pH. In this study, we aimed to investigate the prognostic potential of oropharyngeal pH monitoring to predict responsiveness to PPI therapy in patients with laryngeal symptoms.

Methods—We conducted a physician blinded prospective cohort study at a single academic institution between 1/2013–10/2014. Adult patients with Reflux Symptom Index scores (RSI) ≥ 13 off PPI therapy were recruited. Patients underwent video laryngoscopy and 24-hour oropharyngeal pH monitoring, followed by an 8–12 week trial of omeprazole 40 mg daily. Prior to, and following PPI therapy, patients completed various symptom questionnaires. The primary outcome was the association between PPI response and oropharyngeal pH metrics. PPI response was separated into three subgroups based on post-treatment RSI score and % RSI response: Non-response = RSI ≥ 13 ; Partial response = post-treatment RSI < 13 and change in RSI $< 50\%$; and Complete response = post-treatment RSI < 13 and change in RSI $\geq 50\%$. The primary analysis utilized a multinomial logistic regression controlling for pre-treatment RSI score. A secondary analysis assessed the relationship between change in RSI (post-pre) and oropharyngeal pH metrics via ordinary least square regression.

Results—Thirty-four patients completed the study and were included in final analysis. Symptom response to PPI therapy was as follows: 50% no response, 15% partial-response and 35% complete-response. Non-responders had a higher pre-treatment RSI ($P < 0.01$). There were no significant differences in oropharyngeal acid exposure (below pH of 4.0, 5.0, 5.5, 6.0 and RYAN scores) between responder types. The secondary analysis noted a trend between lower PPI response and greater total percent time below pH of 5.0 ($P = 0.03$), upright percent time below pH of 5.0 ($p = .07$) and RYAN supine (corrected) ($P = 0.03$), as well as an association between PPI response and greater decreases in the Anxiety Sensitivity Inventory ($P < 0.01$), Brief Symptom Inventory-18 ($P < 0.01$), and Negative Affect Scale ($P < 0.01$).

Discussion—Oropharyngeal pH testing did not predict laryngeal symptom response to PPI therapy. Contrary to hypothesis, our study signaled that the degree of oropharyngeal acid exposure is inversely related to PPI response. In addition, reduction in negative affect and psychological distress parallels PPI response.

Keywords

Extraesophageal reflux; Laryngopharyngeal reflux; Gastroesophageal reflux; Oropharyngeal pH testing

Introduction

Discerning whether patients with laryngeal symptoms will respond to proton-pump inhibitor (PPI) therapy is clinically challenging. Although chronic laryngitis due to gastroesophageal reflux, referred to as laryngopharyngeal reflux (LPR), is an established extraesophageal reflux syndrome, there exists significant controversy about the causative role of reflux and the clinical algorithm for LPR.^{1, 2} Current methods to detect LPR and predict response to

treatment are of limited utility.^{3, 4} While commonly utilized, laryngoscopy is nonspecific and the reflux finding score (RFS), a validated laryngoscopic diagnostic tool to semi-quantify severity of findings, suffers from poor inter-rater reliability.^{5, 6} Similarly, 24-hour dual probe ambulatory pH monitoring lacks sensitivity and specificity, with concerns over placement variability.⁷ Though an area of interest, outcome studies are lacking for combined pH impedance monitoring and its clinical significance is currently undefined.^{1, 8} In the setting of unreliable diagnostic tests, empiric PPI trials are commonly used to assess for symptom response. However, less than half of patients will respond to PPI therapy, with no significant improvement when compared to placebo.^{9–11} The deficiency of a well-defined clinical algorithm for LPR often results in overutilization of PPI therapy and diagnostic tests. The reported cost of diagnosing and managing extraesophageal reflux is estimated at \$5,000 per patient, and actual cost burden is likely even greater. This is a major healthcare issue as LPR is an increasingly diagnosed entity, postulated to comprise up to 50% of laryngeal complaints in an otolaryngology practice alone.^{4, 12}

The Restech Dx-pH system (Respiratory Technology Corporation, San Diego, CA, USA) is a minimally invasive oropharyngeal pH monitoring device which detects pH in both liquid and aerosolized droplets.^{13, 14} Studies demonstrate that oropharyngeal pH monitoring is highly sensitive in detecting acid reflux in the posterior oropharynx and more quickly reaches pH equilibrium compared to a standard pH catheter.^{13–16} However, data evaluating the agreement between esophageal pH impedance and oropharyngeal pH are mixed^{17–20}, and unified normative values for oropharyngeal pH monitoring are lacking, limiting its current role as a diagnostic tool.^{21–24} In addition, whether oropharyngeal pH testing is a reliable prognostic tool for medical therapy and surgical outcomes is of great interest.¹⁵

This study aimed to determine if oropharyngeal pH monitoring predicts PPI response in patients with laryngeal symptoms. We hypothesized that patients with higher oropharyngeal acid exposure would be more likely to respond to PPI therapy.

Methods

Setting & Subjects

We conducted a prospective observational cohort study at an academic medical center between January 2013 and October 2014. The Institutional Review Board approved the study and a [ClinicalTrials.gov](https://clinicaltrials.gov) record was maintained ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT01755221). Patients between the ages of 18 and 89 presenting to the otolaryngology clinic for a standard of care evaluation for laryngeal symptoms were recruited to participate. Eligible patients had symptoms classically associated with LPR for greater than one month and a total Reflux Symptom Index (RSI) score greater than or equal to 13.⁶ Patients were excluded if PPI use was contraindicated or if they were currently taking a PPI and unable or unwilling to stop the medication for a minimum of two weeks before oropharyngeal pH probe placement. Patients were also excluded if they were pregnant, unable to stop anticoagulant use, or unwilling or unable to undergo an oropharyngeal pH assessment.

Study Design

Patients received a flexible fiber optic video laryngoscopy as part of their standard of care evaluation and the RFS was collected. Patients completed several self-administered questionnaires to obtain a baseline assessment of LPR symptom severity and duration, GERD symptom frequency, and symptom-specific anxiety, discomfort, affect, and stress. The questionnaire set included the RSI, a validated patient-reported laryngeal symptom questionnaire,^{6, 25} GerdQ, a validated instrument for evaluating GERD symptoms,²⁶ Visceral Sensitivity Index (VSI), a validated instrument for gastrointestinal symptom-specific anxiety,²⁷ and the Brief Symptom Inventory (BSI-18), a validated psychosocial self-report symptom scale.¹⁷ In addition, the Heartburn Vigilance Scale (HVS), adapted from the validated Pain Vigilance and Awareness Questionnaire, and the Heartburn Catastrophizing Scale (HCS), adapted from the Pain Catastrophizing Scale were used to examine reflux-specific thought and discomfort.^{28, 29} The Anxiety Sensitivity Inventory (ASI), a validated instrument that assesses beliefs about the social and somatic consequences of anxiety symptoms, and the Discomfort Intolerance Scale (DIS), a self-report measure of the ability to tolerate uncomfortable sensations, were used to evaluate gastrointestinal symptom-specific anxiety.^{30–32} Patients also completed the Positive and Negative Affect Schedule, a valid measure of positive and negative affect and the Perceived Stress Scale-4 (PSS-4), a shortened version of the Perceived Stress Scale, a validated measure of global perceived stress in relation to health outcomes.^{33–36}

Patients underwent oropharyngeal pH assessment with the Restech Dx-pH system. Members of the research team prepared the device by calibrating it at pH levels of four and seven according to the manufacturer's instructions. The pH probe was placed transnasally with the probe resting one cm below the uvula as recommended by the manufacturer. Patients were instructed to carry out their usual routine while the probe was in place, with the exception of vigorous physical activity. Patients recorded symptom events such as coughing, heartburn, and throat clearing in a written diary and on a wireless transponder they carried with them during the assessment period. The next day (24 hours later), patients returned to the clinic for probe removal. Studies were excluded if less than 16 hours of analyzable data was available. In a blinded fashion, physicians analyzed the oropharyngeal pH tracings according to manufacturer recommendations.

After probe removal, patients initiated an eight to twelve week course of omeprazole 40mg daily, thirty minutes prior to the final meal of the day, per the otolaryngology standard of care practice at our institution. At the conclusion of the PPI therapy course, patients returned for a standard of care follow-up visit and completed the aforementioned questionnaire set to obtain a post-PPI therapy assessment of symptom burden.

Definitions

Currently there is no standard definition of PPI response for LPR; thus, PPI response was defined by separating patients into sub-groups based on percent response and post-treatment RSI scores. Non-response was defined as post-treatment RSI \geq 13; Partial response was defined as a post-treatment RSI $<$ 13 but a percent change in RSI $<$ 50%; and Complete response was defined as a post-treatment RSI $<$ 13 and percent change in RSI \geq 50%.

Outcomes

The primary outcome was the association between PPI response and oropharyngeal pH testing parameters. Oropharyngeal pH tracings were analyzed at pH levels of 4.0, 5.0, 5.5, and 6.0 in the upright position and over the total time period. Based on a previous study, which detected a post-supine lag artifact with the software, adjustments were made to calculate corrected time below pH 5.5 in total and upright positions.³ Additionally, composite scores for oropharyngeal pH testing (RYAN scores) were calculated in the upright and supine positions.²²

The secondary outcomes were the associations between PPI response and psychosocial questionnaire results, including baseline and change (post-pre) results.

Statistical Analysis

The primary analysis evaluated PPI response as a dependent variable, considering patients in three sub-groups: Non-responder, Partial responder, and Complete responder. Differences in baseline clinical variables, oropharyngeal pH testing and questionnaire data were analyzed via Chi Square analysis for categorical variables and multinomial logistic regression.

In addition, we performed a secondary analysis to assess the relationships between change in RSI score (post-pre) and baseline clinical variables, oropharyngeal pH testing and questionnaire data via an ordinary least square (OLS) regression. Hypothetically, the OLS regression may identify associations that were obscured in the categorical primary analysis.

Baseline RSI was used as a covariate in each generalized logit and multiple linear regression model. Each outcome variable was tested in a separate model. Since we did not adjust for multiple hypothetical tests, *P*-values less than 0.01 were considered significant and *P*-values between 0.01–0.10 were considered marginally significant. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Multinomial logistic was run using PROC LOGISTIC with the GLOGIT link function for generalized logit.

Results

Of 236 patients with suspected LPR screened for the study, 29 did not meet inclusion criteria and 110 met exclusion criteria. Of the 97 eligible patients, 42 (43.3%) consented and enrolled. The thirty-four (81%) of the 42 patients who had 16 to 24 hours of analyzable oropharyngeal pH data and completed the appropriate questionnaires after PPI therapy were included in the final analysis. [Figure 1]

Baseline Findings

Twenty-four (71%) patients were female gender with an overall mean age of 45.5 ± 13.3 years and mean BMI of 27.2 ± 6.9 kg/m². Commonly presenting symptoms included throat clearing (79.4%), post-nasal drip (79.4%), hoarseness (70.6%), chronic cough (55.9%), globus (47.1%), dysphagia (29.4%), chronic sore throat (23.5%), and difficulty breathing (20.6%). Less than one-third of patients complained of heartburn (32.4%). The overall mean RSI was 23.2 ± 7.3 , with a mean GerdQ of 3.8 ± 4.2 . Laryngoscopy findings were recorded for 19 patients, with a mean RFS of 7.9 ± 2.7 .

Rates of PPI Response

Overall, the mean change (post-pre) in RSI score was a decrease of 8.9 ± 9.2 points, and mean percent change in RSI was reduction by $37.0 \pm 39.7\%$. Seventeen (50%) were non-responders, while 5 (15%) met the definition for partial response and twelve (35%) for complete response [Figure 2]. Baseline clinical variables between these three subgroups did not significantly differ; however, 88% of non-responders were female while 40% of partial responders and 58% of complete responders were female ($P = 0.06$). Additionally, only two patients were smokers and both did not respond to PPI therapy [Table 1].

Pre-treatment Variables

The pre-treatment RSI score was significantly higher in the non-responder group ($P < 0.01$); as such pre-RSI was considered a covariate in study analyses. Differences in pre-treatment psychosocial questionnaire responses were not significant in primary or secondary analyses.

Oropharyngeal pH testing—There were no significant differences in baseline oropharyngeal acid exposure between the three sub-groups in primary analysis. Table 2 depicts the data for oropharyngeal pH measurements below pH values of 5.0, 5.5 (corrected) and RYAN scores (corrected); additional pH descriptive data are presented in the Supplemental Table. In secondary (OLS) analysis, we noted a trend between lower PPI response and greater total percent time below pH of 5.0 ($P = 0.03$), upright percent time below pH of 5.0 ($P = 0.07$) and RYAN supine (corrected) ($P = 0.03$); otherwise no significant associations were detected.

Post-treatment Variables

Changes in GerdQ were not associated with PPI response. In secondary analysis (OLS regression), PPI response was associated with greater decreases in ASI ($P < 0.01$), BSI-18 ($P < 0.01$), Negative Affect Scale ($P < 0.01$), and PSS4 ($P < 0.04$); these trends were not significant in the primary analysis (generalized logit model). PPI response was not associated with changes in DIS, VSI, HVS, or HCS in both analyses [Figure 3].

Discussion

In this physician-blinded prospective observational cohort study, neither oropharyngeal pH testing nor pre-treatment psychosocial factors predicted laryngeal symptom response to PPI therapy, and our results do not support the use of these as clinical surrogates for predicting response to PPI therapy.

Contrary to our hypothesis that greater acid exposure would predict PPI response, our secondary analysis (OLS regression) suggested that a higher oropharyngeal acid burden (defined as less than pH level of 5.0) exists for PPI non-responders. Although not found in primary analysis when comparing responder types, this phenomenon is thought provoking, suggesting that those with higher acid exposure between pH of 4.0 to 5.0 are increasingly refractory to the therapeutic benefits of PPI therapy. Perhaps this reflects that the laryngopharynx is most sensitive to exposure below pH levels of 5.0, and that PPIs are less effective in reducing pH below this level. As seen in our prior study, an oropharyngeal pH

level of 5.0 in the context of laryngeal symptoms appears to be most discriminatory, and further work to determine thresholds at this pH level are needed.³ Despite this relationship, there was an absence of measurable events below a pH level of 5.0 in the majority of PPI non-responders. As expected, higher pre-treatment RSI scores were associated with PPI non-response, suggesting that severity of initial symptoms is associated with refractoriness to PPI treatment.

Our findings differ from other studies examining the relationship between oropharyngeal pH testing and PPI response. In a retrospective case control study of 170 patients with LPR symptoms, Friedman et al. reported that PPI therapy based on a positive RYAN score compared to empiric PPI therapy resulted in significantly increased symptom response and compliance to therapy; however, in both the control and case groups the RSI significantly decreased following treatment, with mean post-treatment RSIs less than 13.³⁷ A prospective study of 22 patients with LPR symptoms reported a 59% response rate to PPI therapy, and described that oropharyngeal pH testing has a 69% sensitivity and 100% specificity for predicting PPI response. However, response was defined as at least a 5-point decrease in RSI; derivation of this 5-point decrease threshold is unclear. Furthermore the statistical model did not control for pre-RSI or examine percentage change in RSI or RSI thresholds.³⁸ These studies, including ours, highlight the need for clarifying thresholds and normative values for oropharyngeal pH testing and RSI prior to studying the predictive role of oropharyngeal pH testing. In particular, we previously found that one-third of healthy volunteers manifested abnormal upright RYAN scores, questioning the validity of the RYAN score and urging reexamination of normal and abnormal cutoff values.²⁴ In an attempt to circumvent these issues our study defined response based on RSI thresholds and response rates reported in the literature, and additionally conducted a secondary analysis to examine associations. Moreover, our analysis assessed percent time of oropharyngeal acid exposure in place of normative thresholds.

The question of whether GERD is a co-factor in LPR remains unanswered. PPI responders in our study did not have higher initial GerdQ nor heartburn vigilance or heartburn catastrophizing scores than non-responders, suggesting that all patients with laryngeal symptoms who derive benefit from PPI therapy do not have classic co-morbid GERD. Factors beyond acidic gastroesophageal reflux are known to contribute to laryngeal pathology. For instance, allergen exposure is related to supraglottic eosinophilia.³⁹ Work in esophageal eosinophilia suggests that the therapeutic role of PPIs may extend beyond an antacid mechanism and involve anti-inflammatory properties; future studies should examine the association between laryngeal eosinophilia and PPI response.⁴⁰ Additionally, tobacco is associated with elevated subglottic mucin and smokers are at risk of developing chronic laryngeal disease and cancer outside of their acid exposure.³⁹ Another theory is that acidic reflux is not the primary driver of laryngeal symptoms. Higher salivary pepsin concentrations have been detected in patients with laryngeal complaints without evidence of higher oropharyngeal acid exposure.³ Pepsin is postulated to be a potential biomarker of GERD,⁴¹ and it is possible that either a non-acidic or higher volume of refluxate drives symptoms or that 24-hour monitoring may not capture the original insult.

The role of psychosocial factors in the presentation of laryngeal symptoms is an area of interest. In our study, PPI response paralleled the reduction in psychosocial scores of anxiety, stress and negative affect, however the psychosocial scores did not predict PPI response. Laryngeal hypersensitivity may play a role in symptom recognition in laryngeal irritation, similar to the concept of esophageal hypersensitivity in patients with persistent troublesome GERD symptoms.^{42, 43} At the same time, it is possible that patients enrolled in a clinical trial may be more likely to feel better with regards to health related outcomes, translating to improvements in psychosocial questionnaire results. While this chicken and egg phenomenon is unclear, our results do support the interplay between psychosocial factors and symptom generation. These considerations reiterate the importance of tailoring management to symptom genesis, as PPI therapy as a primary treatment may not be indicated, and therapeutic strategies for certain sub-groups should include cognitive behavioral therapy and neuromodulation.

Although limited by a small sample size, these results suggest that oropharyngeal pH testing is unlikely to have sufficient specificity to replace empiric PPI therapy in the initial treatment algorithm for patients with suspected LPR. Furthermore, this study was not designed to measure the actual effect of PPI therapy as on-treatment pH measurements were not performed and this question would be best evaluated in a larger randomized controlled fashion with a placebo arm. Our patients also had low baseline GerdQ scores, and GERD symptom response to PPI therapy was thus difficult to interpret. Finally, we examined several oropharyngeal pH parameters and psychosocial factors which introduces the possibility of familywise error. While none of the pH parameters were strongly statistically significant or would stand up to familywise adjustment, *P*-values should be interpreted cautiously.

In conclusion, our results do not support the use of oropharyngeal pH testing or psychosocial questionnaires to predict symptom response to PPI therapy. This study importantly cautions against clinical reliance on oropharyngeal pH monitoring as a prognostic tool in suspected LPR. Unexpectedly, our study signals that the degree of oropharyngeal acid exposure may be inversely related to PPI response; as such, thresholds and the relationship between acid exposure and PPI response need to be clarified before utilizing this technology to guide management decisions of long-term PPI therapy or antireflux procedures. In addition, further work is needed to understand the mechanisms involved in laryngeal symptom genesis. This study suggests a relationship between laryngeal symptoms and psychosocial factors, providing groundwork for future studies to incorporate these therapeutic targets into clinical algorithms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The exception of: RY: Supported by T32 DK101363-02 grant; JEP: Consults for Covidien, Sandhill Scientific, and Given.

Abbreviations

PPI	Proton-pump inhibitor
LPR	Laryngopharyngeal Reflux
RFS	Reflux Finding Score
RSI	Reflux Symptom Index
VSI	Visceral Sensitivity Index
BSI-18	Brief Symptom Inventory
HVS	Heartburn Vigilance Scale
HCS	Heartburn Catastrophizing Scale
ASI	Anxiety Sensitivity Inventory
DIS	Discomfort Intolerance Scale
PSS-4	Perceived Stress Scale-4
OLS	Ordinary least square

References

1. Hom C, Vaezi MF. Extrasophageal manifestations of gastroesophageal reflux disease. *Gastroenterol Clin North Am.* 2013; 42:71–91. [PubMed: 23452632]
2. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol.* 2006; 101:1900–1920. quiz 1943. [PubMed: 16928254]
3. Yadlapati R, Adkins C, Jaiyeola DM, et al. Abilities of Oropharyngeal pH Tests and Salivary Pepsin Analysis to Discriminate Between Asymptomatic Volunteers and Subjects with Symptoms of Laryngeal Irritation. *Clin Gastroenterol Hepatol.* 2015
4. Francis DO, Rymer JA, Slaughter JC, et al. High economic burden of caring for patients with suspected extrasophageal reflux. *Am J Gastroenterol.* 2013; 108:905–911. [PubMed: 23545710]
5. Chang BA, MacNeil SD, Morrison MD, et al. The Reliability of the Reflux Finding Score Among General Otolaryngologists. *J Voice.* 2015; 29:572–577. [PubMed: 26118936]
6. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope.* 2001; 111:1313–1317. [PubMed: 11568561]
7. Vaezi MF, Schroeder PL, Richter JE. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. *Am J Gastroenterol.* 1997; 92:825–829. [PubMed: 9149194]
8. Kavitt RT, Yuksel ES, Slaughter JC, et al. The role of impedance monitoring in patients with extrasophageal symptoms. *Laryngoscope.* 2013; 123:2463–2468. [PubMed: 23857711]
9. Noordzij JPAK, Evans BA, Desper E, Mittal RK, Reibel JF, Levine PA. Evaluation of omeprazole in the treatment of reflux laryngitis: A prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope.* 2001; 111:2147–2151. [PubMed: 11802014]
10. El-Serag HBLP, Buchner A, Inadomi JM, Gavin M, McCarthy DM. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. *Am J Gastroenterol.* 2001; 96:979–983. [PubMed: 11316215]
11. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngopharyngitis: a randomized placebo-control trial. *Otolaryngol Head Neck Surg.* 2004; 131:342–350. [PubMed: 15467597]

12. Asaoka D, Nagahara A, Matsumoto K, et al. Current perspectives on reflux laryngitis. *Clin J Gastroenterol*. 2014; 7:471–475. [PubMed: 25491904]
13. Friedman M, Hamilton C, Samuelson CG, et al. The Value of Routine pH Monitoring in the Diagnosis and Treatment of Laryngopharyngeal Reflux. *Otolaryngol Head Neck Surg*. 2012
14. Ayazi S, Lipham JCH, J A, Tang AL, Zehetner J, Leers JM, Oezcelik A, Abate E, Banki F, DeMeester SR, DeMeester TR. A New Technique for Measurement of Pharyngeal pH: Normal Values and Discriminating pH Threshold. *J Gastrointest Surg*. 2009; 13:1422–1429. [PubMed: 19421822]
15. Patel DA, Harb AH, Vaezi MF. Oropharyngeal Reflux Monitoring and Atypical Gastroesophageal Reflux Disease. *Curr Gastroenterol Rep*. 2016; 18:12. [PubMed: 26908280]
16. Yuksel ES, Slaughter JC, Mukhtar N, et al. An oropharyngeal pH monitoring device to evaluate patients with chronic laryngitis. *Neurogastroenterol Motil*. 2013; 25:e315–e323. [PubMed: 23495894]
17. Andrews TM, Orobello N. Histologic versus pH probe results in pediatric laryngopharyngeal reflux. *Int J Pediatr Otorhinolaryngol*. 2013; 77:813–816. [PubMed: 23489887]
18. Chiou E, Rosen R, Jiang H, et al. Diagnosis of supra-esophageal gastric reflux: correlation of oropharyngeal pH with esophageal impedance monitoring for gastro-esophageal reflux. *Neurogastroenterol Motil*. 2011; 23:717–e326. [PubMed: 21592256]
19. Ummarino D, Vandermeulen L, Roosens B, et al. Gastroesophageal reflux evaluation in patients affected by chronic cough: Restech versus multichannel intraluminal impedance/pH metry. *Laryngoscope*. 2013; 123:980–984. [PubMed: 23023943]
20. Becker V, Graf S, Schlag C, et al. First agreement analysis and day-to-day comparison of pharyngeal pH monitoring with pH/impedance monitoring in patients with suspected laryngopharyngeal reflux. *J Gastrointest Surg*. 2012; 16:1096–1101. [PubMed: 22450948]
21. Sun G, Muddana S, Slaughter JC, et al. A new pH catheter for laryngopharyngeal reflux: Normal values. *Laryngoscope*. 2009; 119:1639–1643. [PubMed: 19504553]
22. Ayazi S, Lipham JC, Hagen JA, et al. A new technique for measurement of pharyngeal pH: normal values and discriminating pH threshold. *J Gastrointest Surg*. 2009; 13:1422–1429. [PubMed: 19421822]
23. Chheda NN, Seybt MW, Schade RR, et al. Normal values for pharyngeal pH monitoring. *Ann Otol Rhinol Laryngol*. 2009; 118:166–171. [PubMed: 19374146]
24. Yadlapati R, Adkins C, Jaiyeola DM, et al. Abilities of Oropharyngeal pH Tests and Salivary Pepsin Analysis to Discriminate Between Asymptomatic Volunteers and Subjects With Symptoms of Laryngeal Irritation. *Clin Gastroenterol Hepatol*. 2015
25. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991; 101:1–78.
26. Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther*. 2009; 30:1030–1038. [PubMed: 19737151]
27. Labus JS, Mayer EA, Chang L, et al. The central role of gastrointestinal-specific anxiety in irritable bowel syndrome: further validation of the visceral sensitivity index. *Psychosom Med*. 2007; 69:89–98. [PubMed: 17244851]
28. Roelofs J, Peters ML, McCracken L, et al. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain*. 2003; 101:299–306. [PubMed: 12583873]
29. Osman A, Barrios FX, Gutierrez PM, et al. The Pain Catastrophizing Scale: further psychometric evaluation with adult samples. *J Behav Med*. 2000; 23:351–365. [PubMed: 10984864]
30. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983; 13:595–605. [PubMed: 6622612]
31. RL PRAH. The anxiety sensitivity index: Construct validity and factor analytic structure. *Journal of Anxiety Disorders*. 1987; 1:117–121.

32. Schmidt NB, Richey JA, Fitzpatrick KK. Discomfort intolerance: Development of a construct and measure relevant to panic disorder. *J Anxiety Disord.* 2006; 20:263–280. [PubMed: 16564432]
33. Dietrich M, Verdolini Abbott K, Gartner-Schmidt J, et al. The frequency of perceived stress, anxiety, and depression in patients with common pathologies affecting voice. *J Voice.* 2008; 22:472–488. [PubMed: 18395419]
34. Levenstein S, Prantera C, Varvo V, et al. Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. *J Psychosom Res.* 1993; 37:19–32.
35. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* 1988; 54:1063–1070. [PubMed: 3397865]
36. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol.* 2004; 43:245–265. [PubMed: 15333231]
37. Friedman M, Maley A, Kelley K, et al. Impact of pH monitoring on laryngopharyngeal reflux treatment: improved compliance and symptom resolution. *Otolaryngol Head Neck Surg.* 2011; 144:558–562. [PubMed: 21493235]
38. Vailati C, Mazzoleni G, Bondi S, et al. Oropharyngeal pH monitoring for laryngopharyngeal reflux: is it a reliable test before therapy? *J Voice.* 2013; 27:84–89. [PubMed: 23159026]
39. Mouadeb DA, Belafsky PC, Birchall M, et al. The effects of allergens and tobacco smoke on the laryngeal mucosa of guinea pigs. *Otolaryngol Head Neck Surg.* 2009; 140:493–497. [PubMed: 19328336]
40. Richter JE. Current Management of Eosinophilic Esophagitis 2015. *J Clin Gastroenterol.* 2015
41. Hayat JO, Gabieta-Somnez S, Yazaki E, et al. Pepsin in saliva for the diagnosis of gastro-oesophageal reflux disease. *Gut.* 2015; 64:373–380. [PubMed: 24812000]
42. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. *Neurogastroenterol Motil.* 2015; 27:1667–1674. [PubMed: 26337396]
43. Anderson JA. Work-associated irritable larynx syndrome. *Curr Opin Allergy Clin Immunol.* 2015; 15:150–155. [PubMed: 25961388]

Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- It is difficult to predict which patients with laryngeal complaints will respond to proton-pump inhibitor (PPI) therapy
- Current diagnostic methods are not reliable in detecting laryngopharyngeal reflux
- The Restech Dx-pH system is an oropharyngeal pH monitoring device

2. WHAT IS NEW HERE

- Oropharyngeal pH monitoring with the Restech Dx-pH system did not predict laryngeal symptoms response to PPI therapy
- This study suggested that the degree of oropharyngeal acid exposure is inversely related to PPI response

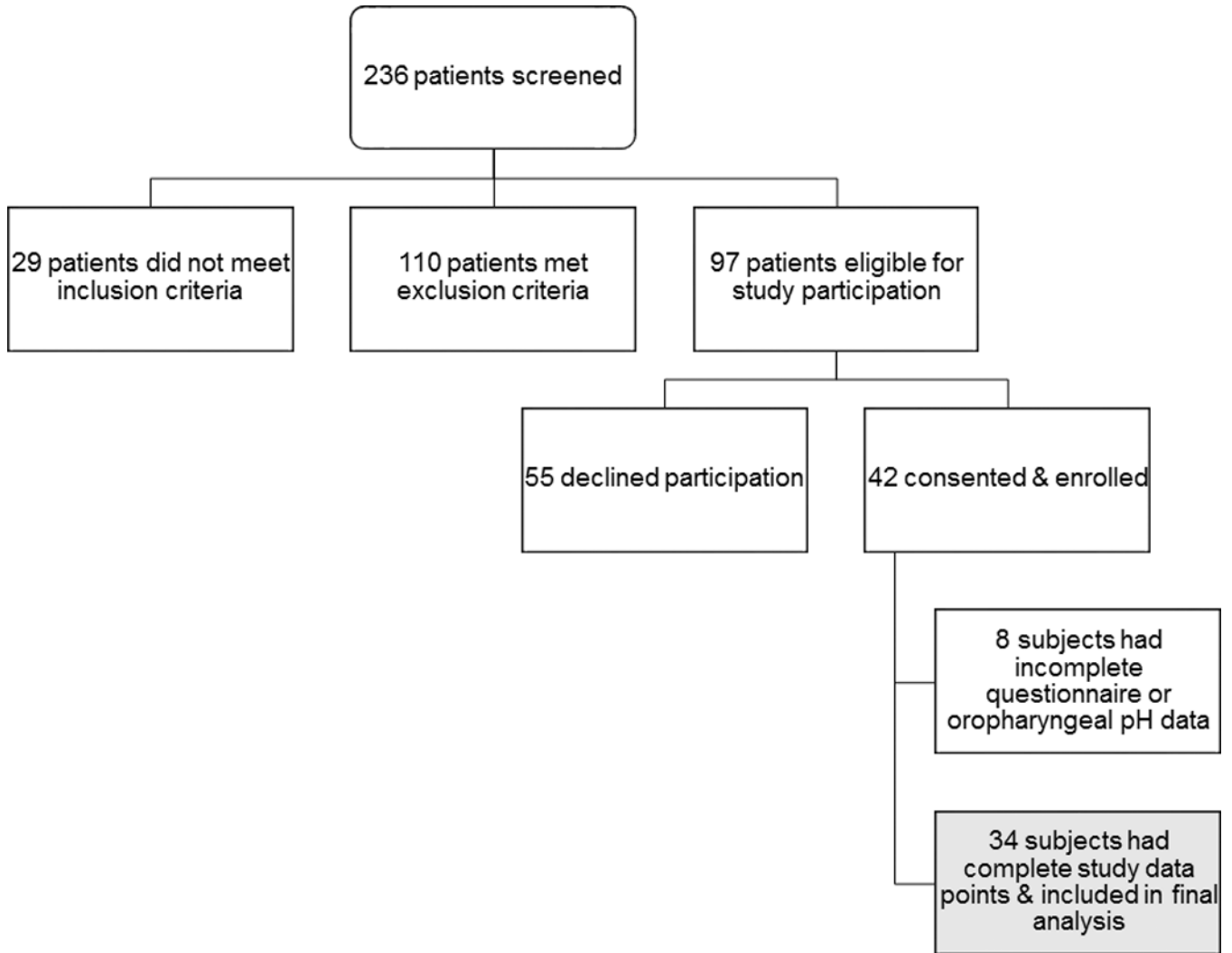


Figure 1. Patient flow diagram

Of 236 patients screened, 139 were not eligible for study participation: 29 did not meet inclusion criteria and 110 met exclusion criteria. Of the 97 eligible patients, 42 (43%) consented & enrolled in the study. Of those enrolled, 34 (81%) had complete study data points and were included in the final analysis.

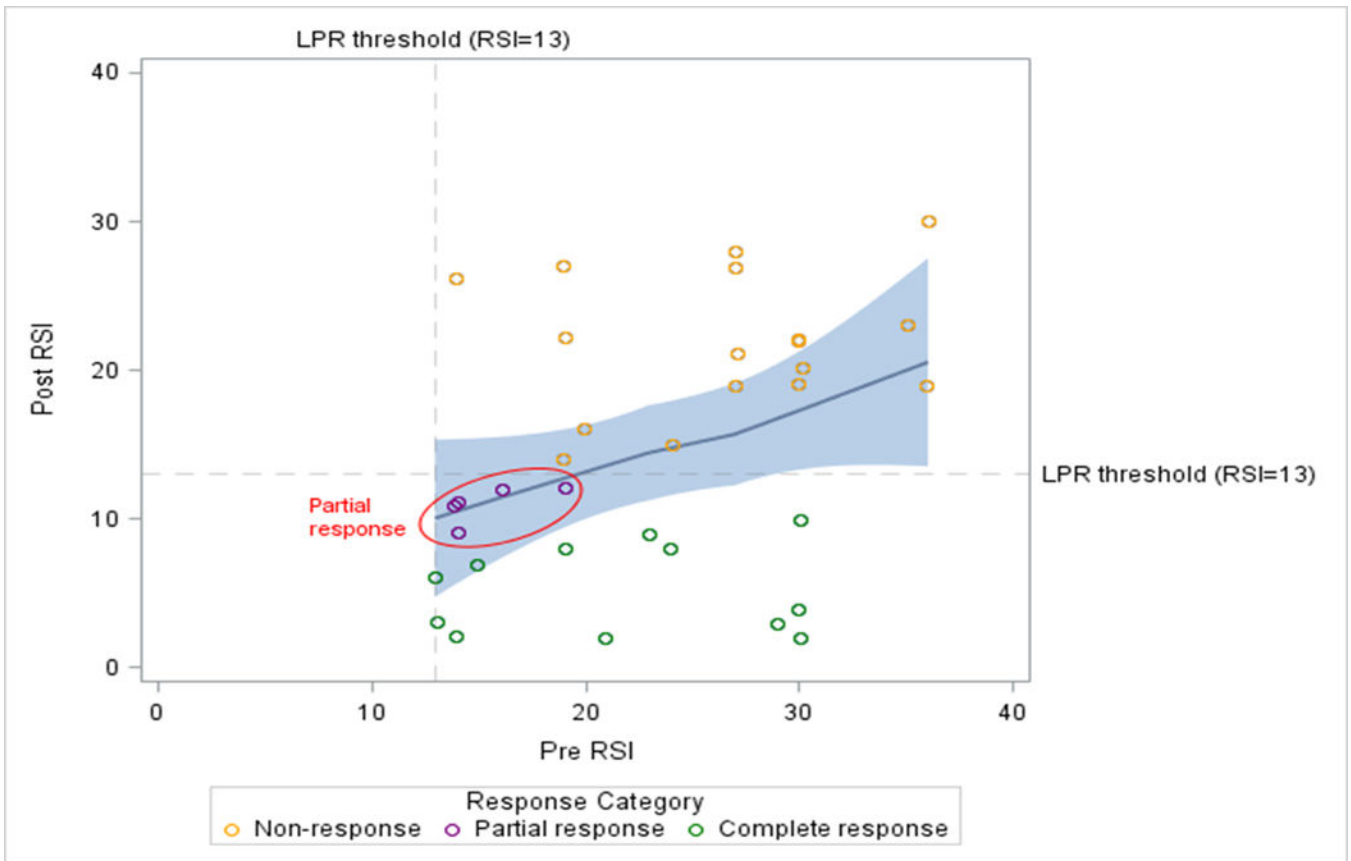


Figure 2. Distribution of patient response type based on pre- and post-RSI scores
Non-response was defined as post-treatment RSI \geq 13; Partial response was defined as a post-treatment RSI < 13 with percent change in RSI < 50%; and Complete response was defined as a post-treatment RSI < 13 with percent change in RSI \geq 50%.

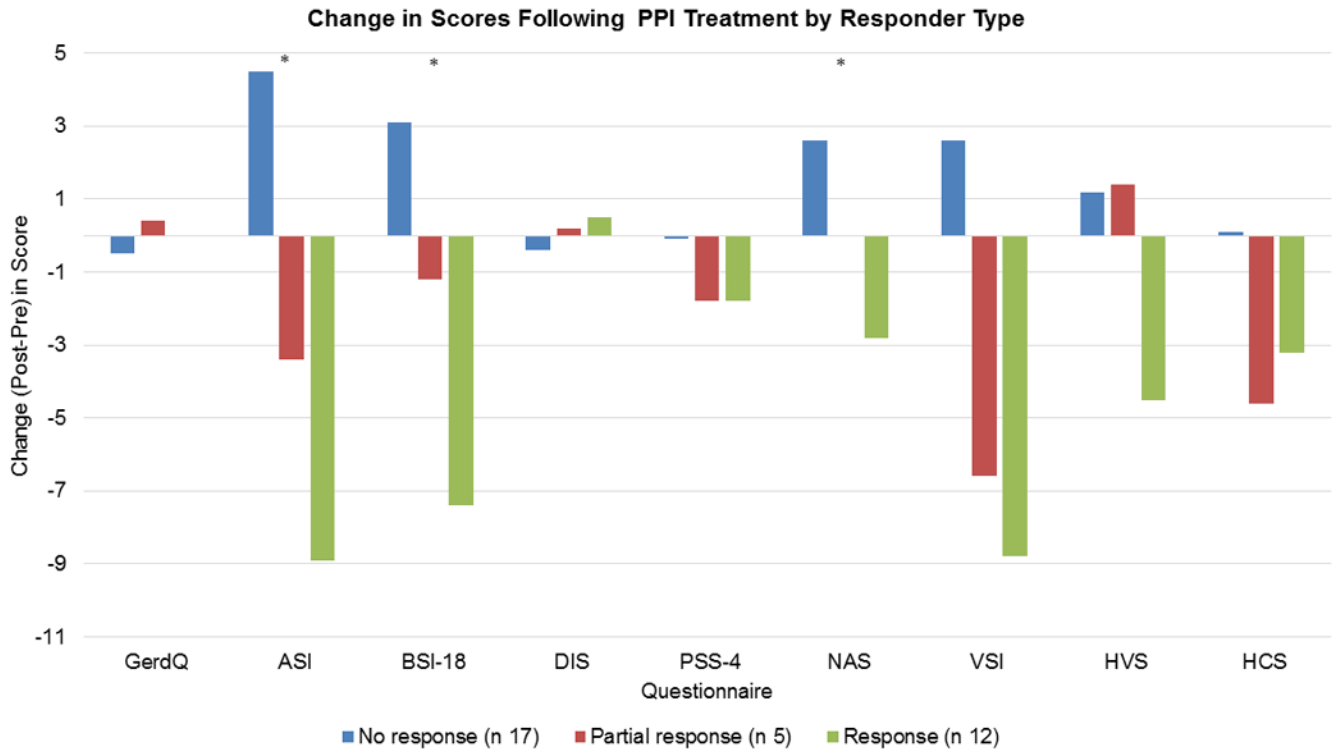


Figure 3. Change in Psychosocial Scores Based on Response Type

In primary analysis, no significant differences were seen in change (post – pretreatment) in psychosocial scores by responder type. In secondary analysis, responders had a significantly greater decrease in ASI, BSI-18 and NAS scores. * indicates $P < 0.01$. Anxiety Sensitivity Inventory (ASI); Brief Symptom Inventory (BSI-18); Discomfort Intolerance Scale (DIS); Perceived Stress Scale-4 (PSS-4); Negative Affect Schedule (NAS); Visceral Sensitivity Index (VSI); Heartburn Vigilance Scale (HVS); Heartburn Catastrophizing Scale (HCS).

Table 1

Baseline clinical data reported for PPI responder group.

	No response (n 17)	Partial response (n 5)	Complete Response (n 12)	P-value
Age (years), Mean (SD)	42.9 (12.1)	47.4 (11.1)	48 (15.9)	0.58
Female Gender, n (%)	15 (88%)	2 (40%)	7 (58%)	0.06
BMI (kg/m ²), Mean (SD)	28.5 (7.30)	25.0 (1.1)	26.4 (7.7)	0.53
Smoker, n (%)	2 (11.8%)	0 (0%)	0 (0%)	0.34
Pre-RSI, Mean (SD)	26.5 (6.5)	15.4 (2.2)	21.8 (6.9)	0.004
Pre-GerdQ, Mean (SD)	3.9 (4.0)	1.4 (1.3)	4.9 (5.0)	0.3
RFS, Mean (SD)	8.3 (3.7)	9.7 (2.1)	7.0 (1.1)	0.3

P-values calculated via generalized logit model with pre-RSI as a covariate.

* Unable to test due to 0 subjects in two groups.

[†]RFS available only for 19 subjects.

Body Mass Index (BMI); Reflux Symptom Index (RSI); Reflux Finding Score (RFS).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Baseline oropharyngeal pH metrics based on PPI response.

Pre-Treatment Oropharyngeal pH Parameters	No response (n 17)	Partial response (n 5)	Complete Response (n 12)	Primary Analysis* P-value	Secondary Analysis† P-value
Total % time pH < 5.0	4.3 (9.2)	1.4 (2.2)	0.4 (0.5)	0.5	0.03
Upright % time pH < 5.0	2.1 (5.4)	3.0 (4.6)	0.4 (0.7)	0.5	0.07
Total % time pH <5.5, Corrected	8.6 (14.8)	11.4 (20.2)	4.0 (4.7)	0.5	0.1
Upright % time pH <5.5, Corrected	3.3 (6.9)	8.5 (17.6)	0.8 (1.0)	0.6	0.2
RYAN Score, Upright, Corrected	130.7 (232.0)	271.0 (535.1)	42.7 (48.4)	0.5	0.2
RYAN Score, Supine, Corrected	10.8 (15.0)	7.4 (11.7)	3.0 (1.6)	0.5	0.03

Both analyses conducted with pre-RSI as a covariate.

* Generalized logit model;

† Ordinary least square regression.