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ALIMENTARY TRACT

Distinct Physiological Characteristics of Isolated Laryngopharyngeal Reflux Symptoms

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BACKGROUND & AIMS: **Patients with isolated laryngopharyngeal reflux symptoms (LPRS) defined as those without concomitant typical reflux symptoms (CTRS) are clinically challenging to manage due to unclear pathophysiology. We investigated esophageal physiology in patients with isolated LPRS and their response to proton-pump inhibitors (PPI) therapy.**

METHODS: **This is a multi-center observational study conducted in referral hospitals in Taiwan. Patients with predominant LPRS, but without common non-reflux causes, underwent esophageal manometry, 24-hr ambulatory esophagopharyngeal pH testing, and Bernstein test, followed by a 12-week esomeprazole 40 mg twice-daily treatment. Participants with pathological reflux were divided into the isolated LPRS group (ie, LPRS without CTRS, n = 40) and the CTRS group (ie, LPRS with CTRS, n = 66). Participants without pathological reflux or esophagitis (n = 132) served as the nonreflux controls.**

RESULTS: **The PPI-responsiveness was similar between the isolated LPRS group and CTRS group (63% vs 57%, $P = .8$), but lower in the nonreflux controls (32%, $P = .005$). Despite similar distal esophageal acid exposure time ($P = .7$) when compared to those with CTRS, the isolated LPRS group had a lower prevalence of both positive Bernstein test ($P = .001$) and ineffective esophageal motility disorder ($P = .03$), and fewer pharyngeal acid reflux episodes ($P < .0001$).**

CONCLUSIONS: **Our findings indicate similar distal esophageal acid exposure and PPI-responsiveness between LPRS patients with and without CTRS. The lack of CTRS in the isolated LPRS group is likely due to esophageal acid hyposensitivity and fewer pharyngeal acid reflux episodes, thus implicating distinct pathophysiology of isolated LPRS from those with CTRS.**

Keywords: Esophageal Motility; Esophageal Hyposensitivity; Pathophysiology.

Abbreviations used in this paper: aOR, adjusted odds ratio; CI, confidence interval; CTRS, concomitant typical reflux symptoms; GERD, gastro-esophageal reflux disease; LES, lower esophageal sphincter pressure; LPRS, laryngopharyngeal reflux symptoms; PAR, pharyngeal acid reflux; PPI, proton pump inhibitor; UES, upper esophageal sphincter.

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Laryngopharyngeal reflux involves reflux of gastric content into the laryngopharynx[1] and is an extraesophageal manifestation of gastroesophageal reflux disease (GERD).[2] Currently, one of the most challenging issues in the management of GERD is treating patients with isolated laryngopharyngeal reflux symptoms (LPRS), defined as GERD without concomitant typical reflux symptoms (CTRS), because there are discrepancies between otolaryngology and gastroenterology guidelines regarding whether these patients should receive acid suppression therapy.[1,3] The gastroenterology guidelines recommend against acid suppression therapy in the absence of CTRS because a meta-analysis consisting of 8 controlled trials failed to demonstrate any treatment benefit[4]; however, the otolaryngology guidelines state that the majority of patients with laryngopharyngeal reflux are without CTRS. The discrepancies may largely be due to the difficulties involved in diagnosing laryngopharyngeal reflux solely on the basis of symptoms or signs and a lack of predictors of treatment response as stated in the recent Lyon Consensus.[5] As a result, empirical therapeutic trials of proton pump inhibitors (PPIs) are commonly used as the initial management approach with a high associated cost in the United States.[6]

Exploring factors predicting treatment response may shed light on the disease pathophysiology and potentially establish a causal link in the absence of a golden standard for diagnosing laryngopharyngeal reflux. In 2013 we proposed a composite pH parameter defined as excessive acid reflux in the pharynx and/or distal esophagus using a 24-hour ambulatory 3-pH-sensor catheter in Taiwanese patients with isolated LPRS.[7] We found that a positive composite pH at 8-week and 12-week time points had a 10-fold and an 8-fold, respectively, likelihood of predicting the response to PPI therapy than a negative composite pH. Recently, Krill et al[8] also found that response to acid suppression therapy may predict response to antireflux surgery. Taken together, these findings suggest that reflux monitoring and response to PPI trials are of value in diagnosing this group of patients.

The mechanisms for symptoms in those presenting with laryngopharyngeal reflux have been proposed to involve either a direct injury to the larynx caused by gastric refluxate (reflux theory) or indirect vago-vagal reflex triggered by acid stimulation in the distal esophagus (reflex theory),[9] yet the physiological features of isolated LPRS remain unclear. Using the composite pH as the diagnostic criterion to define laryngopharyngeal reflux, we investigated the esophageal motor-sensorial features as well as the response to PPI therapy in patients with isolated LPRS compared with those of patients with CTRS and those of patients without reflux (controls).

What You Need to Know

Background

Managing patients with isolated laryngopharyngeal reflux symptoms (LPRS) defined as those without concomitant typical reflux symptoms (CTRS) is challenging because of poorly understood pathophysiology.

Findings

Compared with those with CTRS, patients with isolated LPRS have esophageal acid hyposensitivity and less pharyngeal acid reflux, but they respond equally well to acid suppression therapy, implicating a distinct pathophysiology.

Implications for patient care

Our finding of symptom response to acid suppression therapy in patients with isolated LPRS contradicts the current guidelines that recommend against antireflux treatment in LPRS patients without CTRS.

Methods

Study Design

This was a prospective multicenter cohort study conducted in Taichung Veterans General Hospital, Chung Shan Medical University Hospital, and China Medical University Hospital, Taiwan, involving the Otolaryngology Laboratory, Pulmonology Laboratory, and Gastrointestinal Physiology Laboratory. The protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (#C06254-2) and followed the principle of the Declaration of Helsinki. All participants signed an informed consent form before the study.

Patient Selection

Patients aged between 20 and 70 years referred for otolaryngology consultations between January 2009 and January 2016 were considered for study enrollment. The inclusion criteria were (1) a chief complaint of chronic laryngitis symptoms with at least moderate severity for more than 3 consecutive months before screening and (2) manifestation of laryngoscopic signs suggestive of reflux. Participants were excluded if any common nonreflux etiologies of chronic laryngitis existed (Supplementary Table 1).

Screening Period

Each participant underwent an interview and a series of examinations including a laryngoscopy and an upper gastrointestinal endoscopy to assess eligibility. Participants who met the eligibility criteria underwent esophageal manometry and ambulatory 24-hour esophagopharyngeal

pH monitoring. Each participant identified the most bothersome symptom such as cough, hoarseness, throat clearing, globus, and sore throat as the primary laryngeal symptom at enrollment.[10] Participants were also asked about the type of specialist they first visited for the primary laryngeal symptoms. The presence of CTRS was defined as mild symptoms of heartburn and/or regurgitation occurring ≥2/week or moderate/severe symptoms ≥1/week using a modified international GERD questionnaire.[11]

Esomeprazole Treatment

After the completion of the pH test, the participants were treated with Nexium (AstraZeneca Pharmaceuticals, Södertälje, Sweden) 40 mg 30 minutes before breakfast and 30 minutes before dinner for 12 weeks. Both participants and investigators were blinded to the results of the pH test. During the treatment period, patients' adherence to PPI therapy, adverse events, and concomitant medication were recorded at 4-, 8-, and 12-week follow-up visits.

Treatment Outcome Measures

The primary outcome was the positive response to esomeprazole treatment, defined as ≥50% reduction in primary laryngeal symptoms using a 10-cm visual analog scale (scale: 0 cm, no improvement or worse; 10 cm, 100% improvement) at weeks 4, 8, and 12 during the treatment.[4] The secondary outcome was the patient-reported outcome measures using the GERDyzer measured at baseline and 12 weeks.[12] The GERDyzer has been validated in laryngopharyngeal reflux patients to measure 10-item multidimensional disease-related quality of life by using a 10-cm visual graphic analog scale, with a higher score indicating a worse health-related quality of life.[13]

Laryngoscopy and Upper Gastrointestinal Endoscopy

The same laryngologist (C. C. Wang) performed the nasolaryngoscopy (VNL-1171K; Pentax, Tokyo, Japan) to exclude malignancies of the upper airway and to document laryngeal signs on the basis of the Reflux Finding Score at enrollment.[14] Each participant also underwent upper gastrointestinal endoscopy (GIFXQ-240; Olympus, Tokyo, Japan) to detect the presence of reflux esophagitis, which was defined using Los Angeles classification grade B or higher.

Esophageal Manometry

Esophageal manometry was performed with an 8-channel silicon rubber low-compliance pneumohydraulic perfused manometric assembly (Dentsleeve Pty Ltd, Adelaide, South Australia) after an overnight fast. In the supine position, station pull-through method at 1-cm intervals was used to record the resting pressures and the locations of both the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES) before the pH study.[15] Ten swallows with 5 mL water were performed to record primary esophageal peristalsis. Ineffective esophageal motility was defined as ≥50% ineffective wet swallows (<30 mm Hg) in the distal esophagus 3 and 8 cm above the LES. The Bernstein test for esophageal acid sensitivity was performed by 30-mL infusion of 0.1 N HCl or saline via the manometry catheter into the middle esophagus, in a random order blinded to the subject, for up to 5 minutes.[16] The test was positive if acid perfusion, but not the saline perfusion, provoked symptoms of heartburn or chest pain.

Twenty-four–Hour Ambulatory Esophagopharyngeal pH Monitoring

An ambulatory 24-hour pH catheter incorporating 3 antimony sensors into a bifurcated probe with a single connector or a pharyngeal impedance-pH catheter (Sandhill Scientific, Highlands Ranch, CO) was used to monitor both pharyngeal and esophageal acidic reflux. Manometry was used to position the proximal pH sensor 1 cm above the UES, the distal sensor at 5 cm above the LES, and the middle sensor at 10 cm distal to the proximal one. The pharyngeal impedance-pH catheter was an impedance catheter with 2 sites for pH monitoring (hypopharynx and distal esophagus) and 3 pairs of impedance electrodes (hypopharynx, proximal esophagus, and distal esophagus). The catheter size was selected on the basis of the esophageal length (catheter models ZAI-BL-54, -55, and -56; Sandhill Scientific); this enables the proximal pH probe to be positioned 1 cm above the UES and the distal pH probe at 5 cm (±1 cm) above the LES.

Participants kept a diary including upright and recumbent positions, meal times, and symptoms. A positive symptom index was defined as ≥50% of symptoms of heartburn or chest pain that were temporarily associated with acid reflux within 2 minutes before the onset of symptoms. Subjects remained on their usual diet but excluded acidic beverages, fruit, and any antireflux medications. An abnormal composite pH was defined as the presence of (1) excessive pharyngeal acid reflux (PAR), ie, ≥2 episodes of PAR, and/or (2) excessive distal esophageal acid reflux, ie, ≥4.2% of 24-hour, or ≥6.3% of upright position, or ≥1.2% of supine position, with pH <4 at 5 cm above the upper margin of the LES.[7]

We adopted the strict criterion of PAR developed by Williams et al[17] with slight modification, ie, ≥2 units of pH decrease in pharynx during esophageal acidification that reached a nadir of pH <5 within 30 seconds, which has good interobserver agreement of making a diagnosis of PAR.[18] For 3-pH-sensor interpretations, we excluded meal time periods, liquid swallows outside meal times,

slow pH drift, isolated pharyngeal pH drop, and other artifacts. The identification of PAR was further supported by the proximal esophageal pH sensor, which allows better tracking of true reflux up to the pharynx.[19] For those who underwent pharyngeal impedance-pH catheters, impedance sensors were able to differentiate PAR (retrograde changes) from swallows (antegrade changes). The interpretations were performed with agreement by 2 experienced experts (H.C. Lien and C.S. Chang) who were blinded to the patient's information.

Statistical Analysis

Participants were divided into 3 groups: with isolated LPRS, with CTRS, and nonreflux controls (Figure 1). The composite pH was abnormal in the former 2 groups and normal in the latter one. Demographic data, clinical characteristics, and physiological features were compared among the 3 groups. Kruskal-Wallis tests and Pearson χ^2 tests were used for continuous and dichotomous variables, respectively. The primary outcome was compared between groups by using per-protocol analysis after adjustments for age, sex, body mass index, and the presence of reflux esophagitis. The secondary outcome was compared between groups at baseline and at the end of treatment. Multivariate logistic regression analysis was used to determine the independent factors associated with isolated LPRS. A P value $<.05$ was considered significant.

Results

Baseline Characteristics

After excluding common nonreflux etiologies, 252 of 398 subjects completed the 3-sensor pH (n = 154) or pH-impedance (n = 98) testing. Among them, 106 had pathologic reflux (40 with isolated LPRS, 66 with CTRS), whereas 132 participants without pathologic reflux or reflux esophagitis served as the nonreflux controls (Figure 1). Table 1 shows the baseline characteristics of the study population. The age, gender, and body mass index were comparable between the 2 reflux groups, but the nonreflux controls were slightly younger, showed greater female predominance, and weighed less compared with the 2 reflux groups. The vast majority of participants with isolated LPRS visited otolaryngologists (ENT) for their primary symptoms versus half of those with CTRS. The clinical presentations including the laryngeal symptoms, symptom durations, previous acid suppressive therapy, and comorbidities were similar among the 3 groups. Reflux esophagitis (defined by LA Classification) occurred in one-fourth of the participants

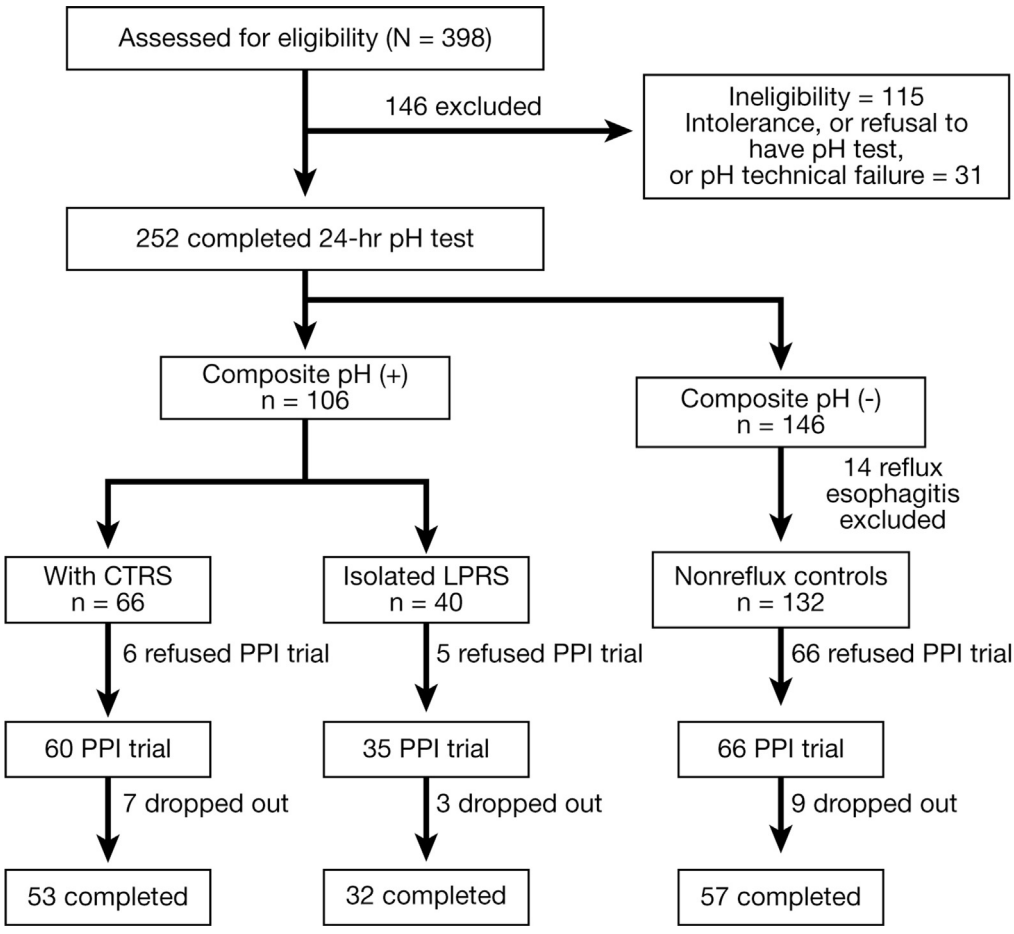

Figure 1. Flow chart of study population enrollment. CTRS, concomitant typical reflux symptoms; PPI, proton pump inhibitor.

Table 1. Baseline Characteristics of the Study Populations

	With CTRS[a] (n = 66)	Isolated LPRS (n = 40)	Nonreflux controls (n = 132)	*P* value 3-group comparison
Demography				
Age (*y*)	53 (44–63)	54 (43–60)[b]	50 (39–58)[c]	.06
Male gender (%)	59	68[b]	46	.03
BMI (kg/m^2)	24.7 (22.7–26.3)	24.0 (21.8–25.8)[b]	22.3 (20.9–24.8)[c]	<.0001
ENT first visit (%)	52[d]	88	81[c]	<.0001
Clinical presentations				
Major laryngeal symptom (%)				
Globus sensation	29	20	34	.2
Throat pain	27	25	20	.5
Hoarseness	17[d]	38	25	.06
Cough	21	13	14	.4
Throat clearing	6	5	7	.9
Symptom duration (*mo*)	18 (9–54)	13 (6–36)	18 (8–36)	.6
Previous acid suppressive therapy use (%)	71	53	58	.1
Diabetes mellitus (%)	3	3	2	.9
Hypertension (%)	23	13	16	.3
Postnasal drip (%)	50	35	35[c]	.1
Endoscopic findings				
Reflux esophagitis (%)	26	25[b]	0[c]	<.0001
Barrett's esophagus (%)	9	5[b]	0[c]	.003
Hiatus hernia (%)	23	13	5[c]	.0005
Peptic ulcer (%)	12	8	17	.2
Helicobacter pylori (%)	27	18	25	.6
Reflux Finding Score[e]	6 (4–8)	6 (3–7)	5 (4–7)	.6
Patient-reported outcome				
GERDyzer total score[f]	42 (21–54)	33 (19–43)	36 (24–49)	.2
Heartburn, frequency[g]	3 (1–5)[d]	0 (0–3)	1 (0–3)[c]	<.0001
Heartburn, severity[g]	3 (2–4)[d]	0 (0–2)	1 (0–2)[c]	<.0001
Acid regurgitation, frequency[g]	4 (2–5)[d]	1 (0–2)[b]	2 (0–3)[c]	<.0001
Acid regurgitation, severity[g]	3 (2–4)[d]	1 (0–2)	2 (0–3)[c]	<.0001

NOTE. Results are expressed as median (interquartile range) unless otherwise noted. Pearson χ^2 tests were used for dichotomous variables, whereas Mann-Whitney *U* tests were used for continuous variables. Kruskal-Wallis tests were used for 3-group continuous variables.

BMI, body mass index; CTRS, concomitant typical reflux syndrome; ENT, ear-nose-throat specialists; GERD, gastroesophageal reflux disease; LPRS, laryngopharyngeal reflux symptoms.

[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.

[b]$P < .05$ for isolated LPRS vs nonreflux control.

[c]$P < .05$ for CTRS vs nonreflux control.

[d]$P < .05$ for CTRS vs isolated LPRS.

[e]Score range from 0 to 26, with higher scores suggesting more severe laryngitis.

[f]Score range from 0 to 70, with higher scores suggesting worse quality of life.

[g]Score range from 0 to 5 for symptom frequency or severity, with higher scores suggesting worse quality of life.

in both reflux groups. Barrett's esophagus and hiatal hernia were more prevalent in participants with CTRS (9.1% and 22.7%), followed by those with isolated LPRS (5% and 12.5%), and the nonreflux controls (0% and 4.6%), respectively.

Response to Proton Pump Inhibitor Treatment

In total, 35 participants with isolated LPRS, 60 participants with CTRS, and 66 nonreflux controls underwent esomeprazole trial, and 32, 53, and 57, respectively, completed the trial (Figure 1). The baseline characteristics were comparable between nonparticipants and participants. Nineteen participants were excluded from the study because of the withdrawal of consent (9 cases), loss of follow-up (4 cases), and protocol violation (6 cases). Esomeprazole was generally well-tolerated, with no severe adverse events requiring emergency care or hospitalization. The most commonly reported adverse events were constipation, dyspepsia, diarrhea, and headache. Median adherence in participants who completed the trials assessed by pill counts was 90% (interquartile range, 85%–100%).

After 12 weeks of esomeprazole therapy for the primary laryngeal symptom, more participants had a treatment response in the isolated LPRS group than in the nonreflux controls (63% vs 32%; adjusted odds ratio [aOR], 4.9; 95% confidence interval [CI], 1.8–13.3; $P = .002$), and the same trend was found in those with CTRS group compared with nonreflux controls (57% vs 32%; aOR, 4.0; 95% CI, 1.7–9.3; $P = .002$). There were no

Table 2. Primary and Secondary Outcomes

	With CTRS[a] (n = 53)	Isolated LPRS (n = 32)	Nonreflux controls (n = 57)	*P* value 3-group comparison
Week 4				
Symptom improvement[b]	30 (0–60)	20 (0–60)[c]	0 (0–30)[d]	.001
≥50% improvement[e] (%)	47	28	25[d]	.03
GERDyzer total score	24.8 (12.2–34.5)	19.7 (7.8–31.2)[c]	30.8 (15.8–44.9)[d]	.01
Week 8				
Symptom improvement[b]	50 (0–80)	50 (30–80)[c]	20 (0–50)[e]	.009
≥50% improvement[e] (%)	53	59[c]	33	.03
GERDyzer total score	15.4 (8.7–26.9)	18.0 (8.0–25.7)[c]	27.7 (15.0–41.2)[d]	.002
Week 12				
Symptom improvement[b]	50 (0–90)	70 (30–90)[c]	20 (0–60)[d]	.003
≥50% improvement[e] (%)	57	63[c]	32[d]	.005
GERDyzer total score	17.4 (7.7–27.4)	15.3 (3.2–26.0)[c]	26.7 (12.5–37.0)[d]	.005

NOTE: Results are expressed as median (interquartile range) unless otherwise noted.
CTRS, concomitant typical reflux syndrome; GERD, gastroesophageal reflux disease; LPRS, laryngopharyngeal reflux symptoms.
[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Percentage of improvement in primary laryngeal symptoms using a 10-cm visual analog scale (scale: 0 cm, no improvement or worse; 10 cm, 100% improvement).
[c]$P < .05$ for isolated LPRS vs nonreflux control.
[d]$P < .05$ for CTRS vs nonreflux control.
[e]Percentage of subjects who experienced at least 50% improvement in primary laryngeal symptom.

differences between participants with isolated LPRS and those with CTRS ($P = .8$) (Table 2). Regarding the GERDyzer scores, both participants with isolated LPRS and those with CTRS had a better quality of life at week 12 than the nonreflux controls (Supplementary Figure 1). The improvement of individual laryngeal symptoms as well as typical reflux symptom scores is shown in Supplementary Tables 2 and 3, respectively.

Acid Exposure in Distal Esophagus and Pharynx

For the distal esophagus, the acid exposure time was comparable between the 2 reflux groups in total 24-hour and upright posture, but slightly lower in the isolated LPRS group compared with the CTRS group in supine posture (Table 3). For the pharynx, the percentage of subjects with ≥2 PAR events and the number of PAR events in both 24-hour and upright posture were significantly lower in the isolated LPRS group compared with those in the CTRS group. The phenomenon remained unchanged when separated by 3-pH-sensor and pH-impedance subgroup analyses. (Table 3, Supplementary Table 4). The isolated LPRS group also had a lower acid exposure time in the proximal esophagus compared with the CTRS group. There were no difference of Reflux Finding Score among 3 groups (Supplementary Table 5).

Antireflux Mechanisms

The manometric findings showed a higher resting pressure of both LES and UES and a lower rate of ineffective esophageal motility disorder in participants with isolated LPRS than those with CTRS. The rate of positive Bernstein test and the rate of positive symptom index in participants with isolated LPRS were significantly lower than those with CTRS (Table 3). There were no differences in these parameters between participants with isolated LPRS and the nonreflux controls.

Multivariate Analysis

Using the participants with CTRS as the reference, the multivariate logistic regression analytic model showed that presence of pathologic PAR (aOR, 0.23; 95% CI, 0.07–0.8; $P = .01$) and positive Bernstein test (aOR, 0.23; 95% CI, 0.08–0.7; $P = .006$) were inversely associated with participants with isolated LPRS after adjustments for age, sex, body mass index, and UES resting pressure.

Discussion

In this prospective observational cohort study of patients with positive pathologic esophagopharyngeal acid reflux (composite pH+), we compared the esophageal motor-sensorial function and PPI treatment response of isolated LPRS patients (ie, without CTRS) with these measures in CTRS and nonreflux control patients. We found that patients with isolated LPRS had similar distal esophageal acid exposure time and PPI responsiveness compared with those in the CTRS group, and the lack of CTRS in isolated LPRS individuals is likely due to esophageal acid hyposensitivity and fewer PAR events. Our study also does not support the existence of excessive laryngopharyngeal reflux mechanisms in isolated LPRS patients, thus implicating distinct pathophysiology of isolated LPRS from those with LPRS with CTRS. In

Table 3. Baseline Physiological Testing

	With CTRS[a] (n = 66)	Isolated LPRS (n = 40)	Nonreflux controls (n = 132)	*P* value 3-group comparison
24-hour pH				
Distal esophagus				
Abnormal[b] (%)	82	93[c]	0[d]	<.0001
% total time pH <4	5.6 (3.3–10.7)	5.1 (4.3–8.4)[c]	0.5 (0.1–1.2)[d]	<.0001
% upright time pH <4	7.6 (3.1–12.4)	8.1 (4.6–11.4)[c]	0.6 (0.2–1.8)[d]	<.0001
% supine time pH <4	0.9 (0.1–6.2)[e]	0.2 (0–2)[c]	0 (0–0)[d]	<.0001
Pharynx				
Abnormal PAR[f] (%)	47[e]	15[c]	0[d]	<.0001
No. of PAR events, total	1 (0–5)[e]	0 (0–1)[c]	0 (0–0)[d]	<.0001
No. of PAR events, upright	1 (0–5)[e]	0 (0–0)[c]	0 (0–0)[d]	<.0001
No. of PAR events, supine	0 (0–0)	0 (0–0)[c]	0 (0–0)[d]	.02
Manometry				
Lower esophageal sphincter (*mm Hg*)	10 (7–15)[e]	13 (10–19)	15 (10–20)[d]	.0004
Upper esophageal sphincter (*mm Hg*)	20 (11–30)[e]	28 (18–40)	27 (20–40)[d]	.002
Ineffective esophageal motility (%)	31[e]	7	13[d]	.02
Esophageal sensation				
Positive Bernstein test (%)	55[e]	20	16[d]	<.0001
Positive symptom index (%)	53[e]	23	15[d]	<.0001

NOTE: Results are expressed as median (interquartile range) unless otherwise noted.
CTRS, concomitant typical reflux syndrome; GERD, gastroesophageal reflux disease; LPRS, laryngopharyngeal reflux symptoms; PAR, pharyngeal acid reflux.
[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Percentage of subjects with abnormal distal esophageal pH defined as percent time pH <4 of ≥4.2% of 24-hour, or ≥6.3% of upright position, or ≥1.2% of supine position.
[c]$P < .05$ for isolated LPRS vs nonreflux control.
[d]$P < .05$ for CTRS vs nonreflux control.
[e]$P < .05$ for CTRS vs isolated LPRS.
[f]Percentage of subjects with abnormal pharyngeal pH defined as ≥2 PAR episodes of 24-hour.

addition, the primary laryngeal symptom response to PPI in both reflux groups was superior to that of the nonreflux controls, indicating the value of determining composite pH to stratify reflux symptoms of patients on the basis of their response to PPI or lack thereof, ie, responders vs nonresponders.

In 2002, the position statement of the American Academy of Otolaryngology stated that laryngopharyngeal reflux differs from classic GERD, because the majority of patients with laryngopharyngeal reflux (1) do not have esophagitis or heartburn, (2) are predominantly upright or daytime refluxers, (3) have normal esophageal motility and esophageal acid clearance, and (4) have a dysfunctional UES, compared with patients with GERD.[1,20,21] Although the physiological characteristics identified in our patients with isolated LPRS were consistent with the former 3 statements, we further found hyposensitivity to acid in the distal esophagus as demonstrated by lower positive rates of both symptom index and Bernstein test, despite the presence of pathologic acid exposure in the distal esophagus (Table 3). This may in part account for the absence of CTRS or "silent reflux" frequently encountered by otolaryngologists. The finding was also consistent with the results of a previous study conducted by Korkmaz et al,[16] who found that laryngopharyngeal reflux patients were less sensitive to acid perfusion than patients with reflux esophagitis.

In an earlier study, ineffective esophageal motility was found to be more common in laryngopharyngeal reflux patients with CTRS than in those with heartburn only.[22] In the present study we found that esophageal primary peristalsis and magnitude of LES and UES resting pressures were impaired in those with CTRS compared with patients with isolated LPRS, whereas these antireflux motility metrics were comparable between patients with isolated LPRS and the nonreflux controls, implying a relatively normal esophageal motility in patients with isolated LPRS (Table 3). The finding of normal motility may account for fewer PAR events, which in turn also contributes to the absence of CTRS in isolated LPRS patients. However, the rarity of PAR events found in patients with isolated LPRS in the present study seems to contradict the conventional concept of using pathologic PAR as a surrogate marker of LPRS.[1] Overall, the alleviation of LPRS by prolonged acid suppression therapy in the present study may corroborate a significant role of vago-vagal reflex[23] or central sensitization[24] in the isolated LPRS group, whereas the direct acid exposure with or without central sensitization may be the dominant mechanism in those with CTRS.

Another important finding of our study is that participants with positive composite pH had a 4-fold to 5-fold increased response to esomeprazole treatment for the primary laryngeal symptom compared with nonreflux controls, regardless of the presence or absence of

CTRS. The treatment effects were further supported by the improvement in health-related quality of life, indicating the potential value of determining composite pH status. Although the Porto consensus recommended ambulatory reflux monitoring for the diagnosis of GERD, its role in extraesophageal GERD remains unproved.[25] Unlike GERD, the interpretation of pH testing in extraesophageal GERD is not straightforward and could be confounded by CTRS or symptoms related to asthma. We previously prospectively evaluated the response to PPI therapy in patients with suspected laryngopharyngeal reflux and found that the predictive value of composite pH in subjects with CTRS (aOR, 3.1; 95% CI, 0.9–10.7; $P = .07$) was much lower than that in those with isolated LPRS (aOR, 7.9; 95% CI, 1.4–44.8; $P = .02$).[7] The coexistence of 2 common disorders (GERD and chronic laryngitis) without a causal association in a subset of patients may explain the lower predictive value of composite pH in patients with CTRS. Furthermore, there was a high prevalence of abnormal acid reflux in asthmatic patients that may in part be due to hyperinflation of the lungs and an increased pressure gradient between the abdomen and thorax, resulting in impaired barrier function.[26] The utility of esophageal pH monitoring and endoscopy was evaluated by Fletcher et al[27] in 128 subjects with predominant extraesophageal GERD symptoms, and they found 81% and 18% had abnormal pH and reflux esophagitis, respectively, suggesting a low sensitivity of endoscopy compared with pH monitoring. Interestingly, they found that the presence of CTRS did not correlate with abnormal esophageal pH, which was consistent with our finding in a subgroup of patients with isolated LPRS who had positive composite pH but no CTRS. Future controlled trials are needed to confirm the contribution of composite pH in the diagnosis of patients with isolated LPRS.

There were some limitations in this study. First, the study was conducted in tertiary centers and only recruited participants from an ethnic Chinese population, and thus there may be limited generalizability to primary care settings and other ethnic groups. However, because objective pH parameters were used as the diagnostic criterion, our study can be used to conduct comparisons with the results of other future studies using the same diagnostic criterion. Second, this is an observational study that needs to be validated in large randomized placebo-controlled trials.

In conclusion, patients with isolated LPRS had a relatively normal esophageal motor function and fewer PAR events and were less sensitive to acid than those with CTRS, implying distinct pathophysiology (ie, indirect vago-vagal reflex). Moreover, patients with positive composite pH, regardless of the presence or absence of CTRS, may be more responsive to PPI therapy than those with negative composite pH, thus shedding light on the diagnostic role of composite pH in patients with suspected isolated LPRS.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.08.064.

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Conflicts of interest
The authors disclose no conflicts.

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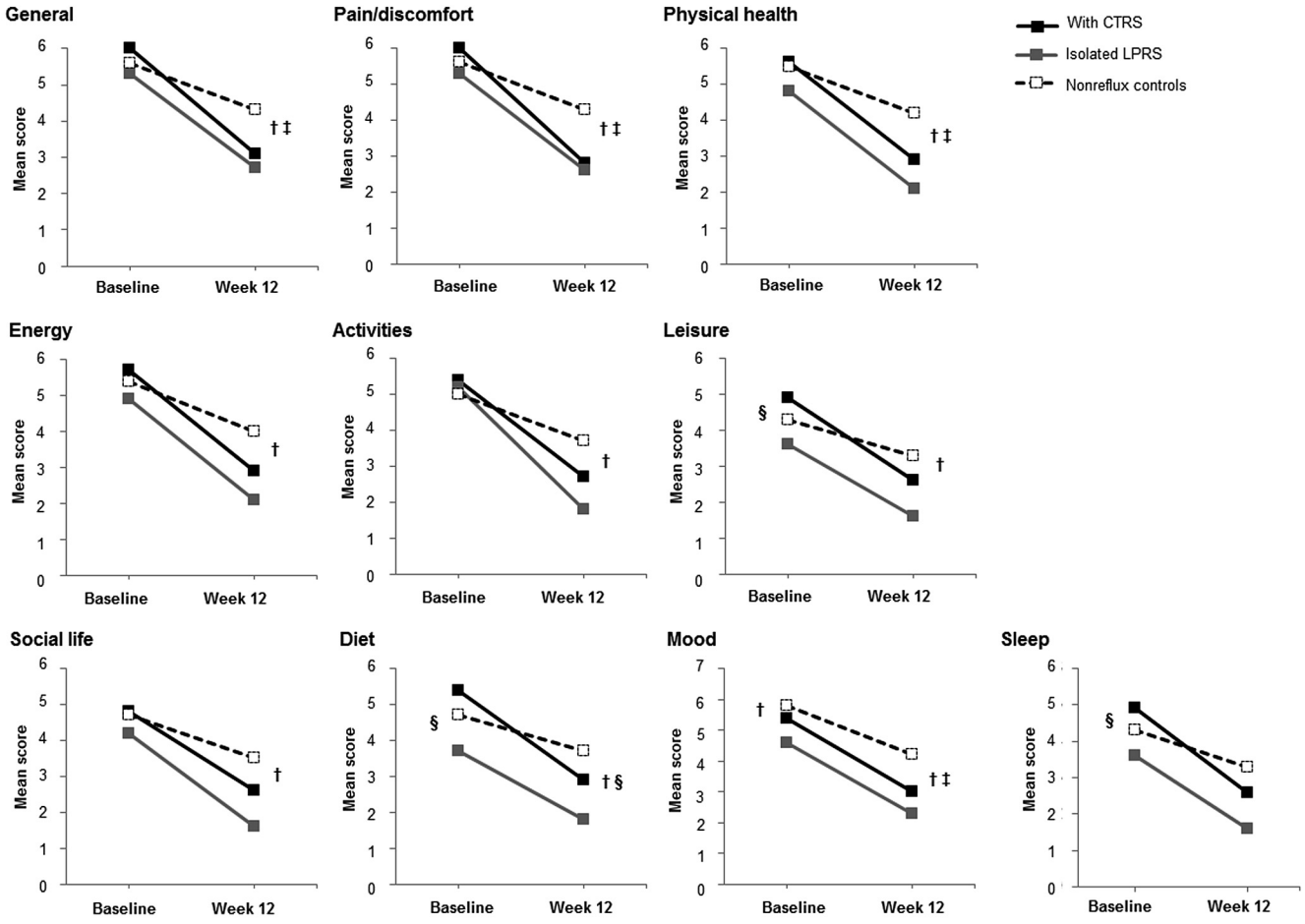

Supplementary Figure 1. Similar response to proton pump inhibitors treatment was observed in both CTRS and isolated LPRS groups for the multi-dimensional health-related quality of life (the GERDyzer). CTRS, concomitant typical reflux syndrome; LPRS, laryngopharyngeal reflux symptoms; PPI, proton pump inhibitor.

Supplementary Table 1. Participants Were Excluded for Any of the Following Conditions

1. Respiratory or gastrointestinal malignancy
2. Receiving radiation therapy, surgery, or trauma for respiratory or upper gastrointestinal tract
3. Current smoker or history of previous heavy smoking or substance or alcohol abuse
4. Infectious laryngitis in the previous 3 months
5. Exposure to environmental irritants in the past 3 months
6. Vocal cord papilloma, enlarged lingual or palatine tonsils, or goiter
7. Excessive voice use
8. Bronchial asthma
9. Chronic cough attributable to angiotensin-converting enzyme inhibitor, or known chronic pulmonary or tracheobronchial etiologies, such as eosinophilic bronchitis, bronchiectasis, positive methacholine provocation test result, or response to inhaled or systemic steroid
10. Pharyngeal (Zenker's) diverticulum or esophageal stasis syndrome, such as achalasia
11. Anxiety or depression with positive response or improvement after 1 month of treatment with an anxiolytic or an antidepressant
12. Chronic or allergic rhinosinusitis, nasal polyposis, or postnasal drip that is responsive to at least 1 month of medical therapy with antihistamine, topical steroid spray, or defined by nasal endoscopy or computed tomography scan
13. Participation in another investigational drug study in the previous month
14. Acid suppressive therapy within 4 weeks before recruitment
15. Need for continuous therapy with theophylline, iron supplements, warfarin, antifungal drugs, and digitalis, or a history of previous allergy to any proton pump inhibitors
16. Women during pregnancy or lactation, or inability to maintain effective contraception if of child-bearing potential
17. A serious illness that might interfere with study participation
18. Inability to fill out the questionnaires or refusal to participate

Supplementary Table 2. Primary Outcomes of Individual Major Laryngeal Symptoms

	With CTRS[a] (n = 53)	Isolated LPRS (n = 32)	Nonreflux controls (n = 57)	*P* value 3-group comparison
Globus sensation				
n	14	6	17	
Week 4				
Symptom improvement[b]	40 (20–50)	5 (0–20)	0 (0–15)[c]	.05
≥50% improvement[d] (%)	50	17	24	.2
Week 8				
Symptom improvement[b]	40 (0–70)	15 (0–40)	0 (0–50)	.3
≥50% improvement[d] (%)	50	17	29	.3
Week 12				
Symptom improvement[b]	25 (0–50)	15 (0–40)	0 (0–30)	.4
≥50% improvement[d] (%)	36	17	12	.3
Throat pain				
n	17	8	12	
Week 4				
Symptom improvement[b]	20 (0–60)	15 (0–60)	55 (0–85)	.6
≥50% improvement[d] (%)	47	25	58	.3
Week 8				
Symptom improvement[b]	35 (0–80)	60 (37.5–85)	60 (0–90)	.7
≥50% improvement[d] (%)	41	63	58	.5
Week 12				
Symptom improvement[b]	60 (0–80)	55 (35–92.5)	70 (25–90)	.8
≥50% improvement[d] (%)	53	63	75	.5
Hoarseness				
n	9	11	16	
Week 4				
Symptom improvement[b]	30 (0–60)	20 (0–50)[e]	0 (0–0)[c]	.01
≥50% improvement[d] (%)	33	27	6	.2
Week 8				
Symptom improvement[b]	50 (20–80)	60 (40–80)[e]	10 (0–40)	.03
≥50% improvement[d] (%)	56	73[e]	25	.04
Week 12				
Symptom improvement[b]	50 (40–90)	80 (60–90)[e]	5 (0–40)[c]	.002
≥50% improvement[d] (%)	67	82[e]	25	.009
Cough				
n	9	5	5	
Week 4				
Symptom improvement[b]	70 (50–90)	40 (30–95)	0 (0–20)[c]	.07
≥50% improvement[d] (%)	78	40	20	.09
Week 8				
Symptom improvement[b]	80 (60–90)	50 (30–90)	30 (0–40)	.3
≥50% improvement[d] (%)	78	60	20	.1
Week 12				
Symptom improvement[b]	90 (50–90)	70 (40–100)	40 (20–40)	.4
≥50% improvement[d] (%)	89	60	20[c]	.04
Throat clearing				
n	4	2	7	
Week 4				
Symptom improvement[b]	15 (5–20)	55 (30–80)	0 (0–30)	.1
≥50% improvement[d] (%)	0	50	14	.3
Week 8				
Symptom improvement[b]	40 (15–60)	70 (60–80)	20 (0–50)	.2
≥50% improvement[d] (%)	50	100	29	.2
Week 12				
Symptom improvement[b]	45 (20–67.5)	85 (80–90)[e]	20 (10–50)	.1
≥50% improvement[d] (%)	50	100	29	.2

NOTE: Results are expressed as median (interquartile range) unless otherwise noted.
CTRS, concomitant typical reflux syndrome; LPRS, laryngopharyngeal reflux symptoms.
[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Percentage of improvement in primary laryngeal symptoms using a 10-cm visual analog scale (scale: 0 cm, no improvement or worse; 10 cm, 100% improvement)
[c]$P < .05$ for CTRS vs nonreflux control.
[d]Percentage of subjects who experienced at least 50% improvement in primary laryngeal symptom.
[e]$P < .05$ for isolated LPRS vs nonreflux control.

Supplementary Table 3. Symptom Scores of Heartburn and Acid Regurgitation[a]

	With CTRS[b] (n = 53)	Isolated LPRS (n = 32)	Nonreflux controls (n = 57)	*P* value 3-group comparison
Week 4				
Heartburn, frequency	1 (0–3)[c]	0 (0–1)	1 (0–3)	.1
Heartburn, severity	1 (0–3)	0 (0–2)	1 (0–2)	.6
Acid regurgitation, frequency	2 (1–3)[c]	0 (0–1)[d]	2 (0–3)	.002
Acid regurgitation, severity	2 (1–3)[c]	1 (0–1)[d]	1 (0–3)	.004
Week 8				
Heartburn, frequency	1 (0–2)	0 (0–1)	1 (0–3)	.1
Heartburn, severity	1 (0–2)	0 (0–1)	1 (0–2)	.5
Acid regurgitation, frequency	1 (0–3)[c]	0 (0–1)[d]	1 (0–3)	.001
Acid regurgitation, severity	1 (1–2)[c]	0 (0–1)[d]	2 (0–2)	.002
Week 12				
Heartburn, frequency	0 (0–2)[c]	0 (0–0)[d]	0 (0–3)	.04
Heartburn, severity	0 (0–2)[c]	0 (0–0)[d]	1 (0–2)	.01
Acid regurgitation, frequency	1 (1–2)[c]	0 (0–0)[d]	1 (0–3)	.0001
Acid regurgitation, severity	1 (1–2)[c]	0 (0–0)[d]	1 (0–3)	<.0001

NOTE: Results are expressed as median (interquartile range).
CTRS, concomitant typical reflux syndrome; LPRS, laryngopharyngeal reflux symptoms.
[a]Score range from 0 to 5 for symptom frequency or severity, with higher scores suggesting worse quality of life.
[b]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[c]$P < .05$ for CTRS vs isolated LPRS.
[d]$P < .05$ for isolated LPRS vs nonreflux control.

Supplementary Table 4. Twenty-four–Hour pH Findings Separated by 3-pH-sensor and Impedance-pH

	With CTRS[a]		Isolated LPRS		Nonreflux controls	
	3-pH-sensor catheter (n = 46)	Impedance-pH catheter (n = 20)	3-pH-sensor catheter (n = 19)	Impedance-pH catheter (n = 21)	3-pH-sensor catheter (n = 81)	Impedance-pH catheter (n = 51)
Distal esophagus						
Abnormal[b] (%)	83	80[c]	84	100	0	0
% total time pH <4	6.9 (3.7–10.7)	4.5 (2.1–9.2)	4.7 (3.5–7.9)	6.0 (4.5–9.2)	0.4 (0.2–0.9)	0.6 (0.1–1.3)
% upright time pH <4	8.5 (4.6–14.3)	6.5 (2.8–9.1)	7.5 (4.4–11.2)	8.1 (6.3–11.5)	0.6 (0.3–1.3)	1.0 (0.1–2.0)
% supine time pH <4	1.0 (0.1–6.6)[d]	0.7 (0.2–4.0)	0.0 (0.0–1.8)	0.9 (0.0–2.1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Proximal esophagus						
% total time pH <4	0.5 (0.2–1.6)[d]	—	0.1 (0.0–0.9)	—	0.0 (0.0–0.1)	—
% upright time pH <4	0.4 (0.3–1.3)	—	0.1 (0.1–1.3)	—	0.0 (0.0–0.2)	—
% supine time pH <4	0.0 (0.0–0.3)	—	0.0 (0.0–0.0)	—	0.0 (0.0–0.0)	—
Pharynx						
Abnormal PAR[e] (%)	43	55 [c]	21	10	0	0
No. of PAR events, total	1 (0–4) [d]	2 (0–7) [c]	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
No. of PAR events, upright	1 (0–3) [d]	2 (0–7) [c]	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
No. of PAR events, supine	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

NOTE. Results are expressed as median (interquartile range) unless otherwise noted.
CTRS, concomitant typical reflux syndrome; LPRS, laryngopharyngeal reflux symptoms; PAR, pharyngeal acid reflux.
[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Percentage of subjects with abnormal distal esophageal pH defined as percent time pH <4 of ≥4.2% of 24-hour, or ≥6.3% of upright position, or ≥1.2% of supine position.
[c]$P < .05$ for CTRS vs isolated LPRS by impedance-pH catheter.
[d]$P < .05$ for CTRS vs isolated LPRS by 3-pH-sensor catheter.
[e]Percentage of subjects with abnormal pharyngeal pH defined as ≥2 PAR episodes of 24-hour.

Supplementary Table 5. Baseline Reflux Finding Score by Item

Reflux Finding Score	With CTRS[a] (n = 41)	Isolated LPRS (n = 32)	Nonreflux controls (n = 84)	*P* value 3-group comparison
Ventricular obliteration	0 (0–2)	0 (0–2)	0 (0–2)	.9
Erythema/hyperemia	0 (0–2)	0 (0–2)	0 (0–2)	.7
Vocal fold edema	1 (1–1)	1 (11)	1 (0–1)	.6
Diffuse laryngeal edema	1 (1–2)	1 (1–1)	1 (0–1)[b]	.06
Posterior commissure hypertrophy	1 (1–2)	1 (1–2)	1 (1–2)	.3
Granuloma/granulation	0 (0–0)	0 (0–0)	0 (0–0)	.2
Thick endolaryngeal mucus	0 (0–0)	0 (0–0)	0 (0–0)	.7

NOTE: Results are expressed as median (interquartile range).
CTRS, concomitant typical reflux syndrome; LPRS, laryngopharyngeal reflux symptoms.
[a]CTRS is defined as regurgitation or heartburn at least twice a week with mild symptom or once a week with moderate/severe symptom.
[b]$P < .05$ for CTRS vs nonreflux control.