el texto, como lo hicieron, cuales fueron sus conclusiones

Comparison of patients of chronic laryngitis with and without troublesome reflux symptoms

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Resumen

La enfermedad por reflujo gastroesofagico (ERGE) ha sido ampliamente reconocida como una causa de laringitis cronica que se refiere ha menudo como Sindrome de laringitis por reflujo (RLS). la cual podemos ver que se revierte con la supresion de acido en pacientes con laringitis cronica..

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Rayter

COMPARISON OF PATIENTS OF CHRONIC LARYNGITIS WITH ANDWITHOUT TROUBLESOME REFLUX SYMPTOMS

OPINION

Respecto a este artículo estoy muy de acuerdo ya que la laringe es mucho más susceptible al efecto del reflujo, ya que esta no tiene un mecanismo de protección como el esófago, y además su mucosa es mucho más delgada y delicada, no adaptándose al reflujo.Una de las causas que puedo ocasionar las laringitis crónicas es el contacto frecuente con ácidos e irritantes y en este caso con el reflujo gastroesofágico que no vine siendo más que el contenido acido del estómago hacia el esófago y desde este, hacia la laringe e hipofaringe causando así la inflamación de las vías respiratorias altas llevando así a provocar una disfonía o ronquera con cambio en el tono de la voz. En estos casos se logran solucionar con un tratamiento individualizado y adecuado a la sintomatología del paciente, pudiendo ser los más aconsejables realizar cambio en los hábitos y dieta para reducir el reflujo y medicación para reducir el ácido estomacal.

Tu comentario es muy pobre, en el artículo te señalan cosas que no vimos en clase, de ahí debes notar las diferencias analizarlas y sacar tus conclusiones.

Revisa bien tu ortografía en español.

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GASTROENTEROLOGY

Comparison of patients of chronic laryngitis with and without troublesome reflux symptoms

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Key words
gastroesophageal reflux disease, impedance, laryngopharyngeal reflux, pH monitoring, proton pump inhibitor.

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Abstract

Background and Aim: Little is known about the difference between patients of chronic laryngitis with and without troublesome reflux symptoms. The aim of this study was to compare the clinical characteristics and response to acid suppression between patients of chronic laryngitis with and without troublesome reflux symptoms.

Methods: Consecutive patients with chronic laryngitis were enrolled. The frequency and severity of reflux and laryngeal symptoms were scored. All the patients underwent laryngoscopy, esophagogastroduodenoscopy and 24-h multichannel intraluminal impedance and pH monitoring before receiving rabeprazole 10 mg b.i.d. for 3 months. Mild typical reflux symptoms (heartburn or regurgitation) occurring ≥ 2 days/week or moderate/severe symptoms occurring ≥ 1 day/week were defined as troublesome reflux symptoms.

Results: Compared to patients without troublesome reflux symptoms, those with troublesome reflux symptoms were older and had more episodes of acid and liquid gastroesophageal reflux (GER) and acid and weakly acidic laryngopharyngeal reflux (LPR). They also had higher percentages of both bolus exposure time and acid exposure time of GER and LPR. Patients with troublesome reflux symptoms responded to acid suppression more often at 12 weeks (67.3% *vs* 20.9%, $P < 0.001$) and more rapidly (40.8% *vs* 14.0%, 3 weeks after the start of acid suppression; $P = 0.004$) compared to those without.

Conclusion: Difference in reflux profile of GER and LPR between patients with and without troublesome reflux symptoms could partly explain the discrepancy of response to acid suppression among patients with chronic laryngitis. Acid suppression therapy may provide limited therapeutic benefits to patients of chronic laryngitis without troublesome reflux symptoms.

Introduction

Gastroesophageal reflux disease (GERD) has been widely recognized as a cause of chronic laryngitis, which is often referred as reflux laryngitis syndrome (RLS).[1] It seems that most patients with RLS require more aggressive and prolonged proton pump inhibitor (PPI) treatment to achieve improvement of laryngeal symptoms than those with GERD.[2] However, most placebo-controlled trials and meta-analyses have failed to demonstrate any therapeutic benefit of PPI.[3–9]

Some studies have revealed that the proportion of patients with marked improvement in laryngeal symptoms is significantly higher in patients with GERD compared to those without GERD.[10,11] It appears that patients with and without GERD have distinct underlying pathophysiologies and require different management approaches. However, these studies gave no information about the reflux profile related to the underlying pathophysiology. In addition, a large proportion of patients with troublesome typical reflux symptoms and chronic laryngitis did not have any objective finding of GERD, such as erosive esophagitis or pathological esophageal acid exposure. The underlying pathophysiological mechanism and the efficacy of acid suppression on these patients are still unknown. It would be simpler and more practical for physicians to evaluate whether patients with chronic laryngitis could benefit from acid suppression therapy depending on symptoms rather than the diagnosis of GERD defined by objective exams in our daily clinical practice. Unfortunately, systematic investigations of the difference between patients with chronic laryngitis with and without troublesome reflux symptoms have not been reported yet. So, we have set out to study a carefully selected group of patients with chronic laryngitis, to compare the clinical characteristics, including reflux profile and response rate to acid suppression, between them.

Subjects and methods

Recruitment of patients

Consecutive patients aged between 18 and 70 years attending the Otorhinolaryngology Clinic of the First Affiliated Hospital of Sun Yat-sen University were recruited if they had the chief complaint of sore throat, throat clearing, throat burning, throat dryness, globus or hoarseness of voice ≥ 3 days/week for at least 3 months. They were referred to a single experienced otorhinolaryngologist for a complete examination of the nose, pharynx and larynx. Patients' medical and surgical history was taken. Patients were excluded if they: were professional voice users (e.g. singer, teacher); had an exposure to occupational or environmental pollutants; had any contraindication to rabeprazole, such as known or suspected allergy or sensitivity to any PPI; had a history of respiratory or gastrointestinal malignancy, peptic ulcer disease, radiation therapy to the head and neck, lung, or gastrointestinal tract; had a significant gastroesophageal, laryngeal or tracheal surgery; had chronic sinusitis, chronic rhinitis, an allergic cause of laryngitis, or an acute traumatic event near the larynx; or had tobacco or alcohol abuse in the past year. Other exclusion criteria included presence of an infectious cause of laryngitis in the past 3 months; any PPI, theophylline, or any other investigational compound or participation in another investigational drug study in the past 1 month; need for continuous therapy within 1 week of enrollment with diazepam, phenytoin, mephenytoin, warfarin, anticholinergics, antineoplastics, prostaglandin analogs, H2-receptor antagonists, steroids (inhaled, oral, or intravenous), promotility drugs, and sucralfate. Women were required to be non-pregnant and non-lactating and to maintain effective contraception if of child-bearing potential. All enrolled patients were also required to have laryngoscopically proven laryngitis that was diagnosed in the same way as previously described.[12] This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all the participants.

Study design

This study was a prospective, cohort study with pre-treatment and post-treatment comparison.

Screening period

Eligible patients then underwent a 7-day screening period without treatment, during which they completed a daily diary card on which they assessed their chief laryngeal complaint and reflux symptoms over the past 24 h on a 4-point Likert scale (0 = no, 1 = minor, 2 = moderate, 3 = intensive). Patients must have completed at least 80% of diary entries and had 3 or more days with moderate or intensive symptoms (≥ 2 points) over the last 7 days. The frequency of each symptom was determined with a 5-point scale (0 = none, 1 = 1 day/week, 2 = 2–3 days/week, 3 = 4–5 days/week, 4 = 6–7 days/week). The score of each symptom was calculated by multiplying severity score of each symptom and the frequency score of the respective symptom.[13–15] Mild reflux symptoms (heartburn or regurgitation) occurring ≥ 2 days/week or moderate/severe symptoms occurring ≥ 1 day/week was defined as troublesome reflux symptoms.[1]

Esophagogastroduodenoscopy and ambulatory 24-h MII-pH monitoring

All patients underwent an esophagogastroduodenoscopy (EGD) (Olympus CV 260, Olympus Optical Company, Tokyo, Japan). The degree of erosive esophagitis (EE) was graded according to the Los Angeles classification.[16] Esophageal manometry (CTD synectics, Stockholm, Sweden) was performed to determine the location of the lower esophageal sphincter (LES) and the upper esophageal sphincter (UES). Then ambulatory 24-h multichannel intraluminal impedance and pH (24-h MII-pH) monitoring was performed using a Sleuth System-Multichannel Intraluminal Impedance Ambulatory System (Sandhill Scientific Inc., Highlands Ranch, CO, USA), which includes a portable data logger with impedance-pH amplifiers and a bifurcated impedance-pH catheter (CZAI-B62C47E, Sandhill Scientific Inc.). Impedance was recorded with the catheter that consists of two 2.1-mm diameter polyvinyl sub-catheters; one for recording impedance from the distal esophagus (esophageal sub-catheter) and the other for recording impedance from the proximal esophagus and the larynx (laryngeal sub-catheter). The sub-catheter for the distal esophagus has three electrodes, positioned in such a way that it measured intraesophageal impedance at 3 cm and 5 cm above the upper border of LES. The laryngeal sub-catheter had six electrodes positioned in such a way that the proximal three electrodes measured intralaryngeal impedance at 1 cm and 0 cm above the upper border of UES and the distal three electrodes measured intraesophageal impedance at 5.5 cm and 7.5 cm below the upper border of UES. In addition, the esophageal sub-catheter was incorporated with an antimony pH electrode (esophageal pH electrode) positioned at 5 cm above the upper border of the LES for monitoring esophageal pH value. Similarly, the laryngeal sub-catheter was also incorporated with a pH sensor (laryngeal pH electrode) positioned at 0.5 cm above the upper border of UES for monitoring laryngeal pH value (Fig. 1).

The GER episodes were characterized by the composition of refluxate as liquid, gas and mixed reflux, the definition of which were described previously.[17] All GER episodes were characterized by pH electrode 5 cm above the upper border of LES as acid, weakly acidic, or weakly alkaline in accordance with the consensus.[18] The GER that reached proximally to 5.5 cm below the upper border of UES was defined as proximal GER. LPR was defined if GER reached proximally to 1 cm above the upper border of UES. If LPR occurred simultaneously with laryngeal pH < 4.0, 4.0–7.0 or > 7.0, and the corresponding nadir esophageal pH reached a pH value equal to or lower than the nadir laryngeal pH, it was defined as acid LPR, weakly acidic LPR or weakly alkaline LPR.

For each reflux episode detected by impedance, bolus exposure times for GER, proximal GER and LPR were calculated as the times between the 50% drop in impedance to recovery of impedance baseline for more than 5 s at 5 cm above the upper border of LES, 5.5 cm below the upper border of UES and 1 cm above the upper border of UES, respectively. Bolus exposure (%) for GER, proximal GER or LPR was obtained by addition of the corresponding bolus exposure time divided by the time of monitoring. Acid exposure (%) for GER or LPR was defined as the time for pH < 4 detected by corresponding pH electrode associated with bolus reflux divided by the time of monitoring.

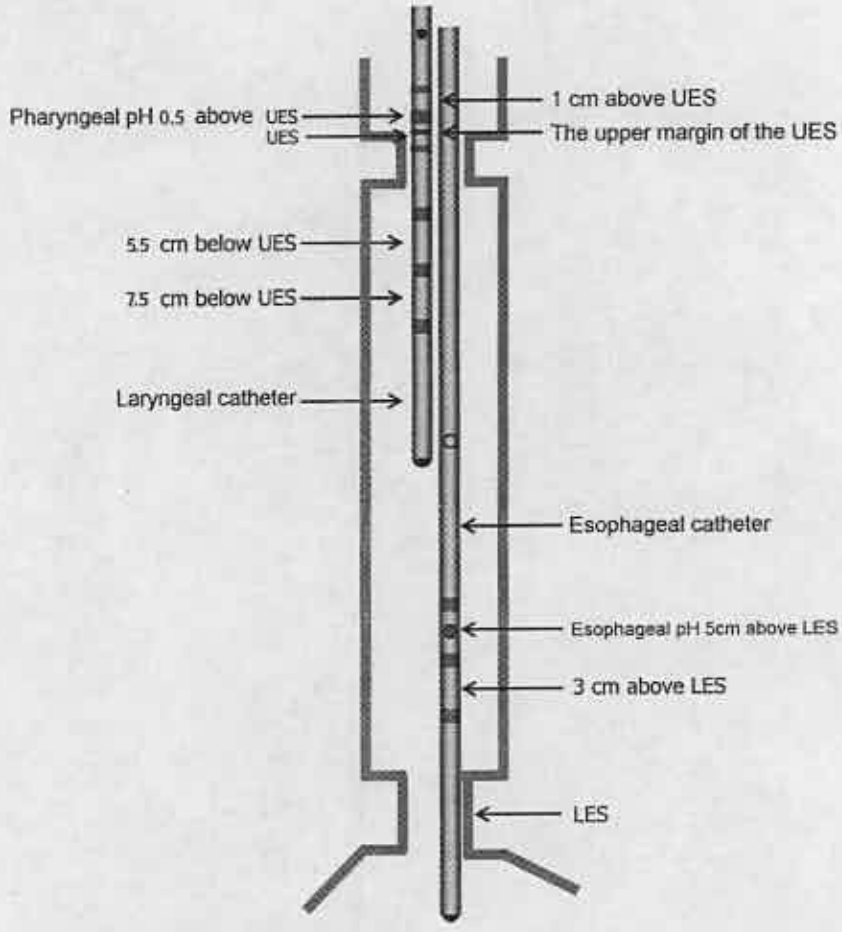

Figure 1 Schematic representation of the recording catheters and their placement.

After intubation, subjects were discharged and encouraged to maintain their normal daily activities, sleep schedules, and mealtimes. The data stored on the CompactFlash card were downloaded onto a personal computer and analyzed visually with the assistance of dedicated software (Bioview Analysis, version 5.0.9; Sandhill Scientific, Inc.). Meals were excluded from the analysis. Pathological acid exposure (PAR) was defined as an intraesophageal pH of < 4, for more than 4% of the recording time. The presence of EE or a pathological acid exposure was defined as GERD.

Treatment schedule

All patients were blinded to the results of EGD and 24-h MII-pH monitoring. After the completion of all examinations, they were told their chronic laryngitis was probably caused by GERD and were given a course of rabeprazole (Pariet, Eisai CO., Ltd, Tokyo, Japan) at a dose of 10 mg 1/2-h preprandial morning and evening meals for 12 weeks. Patients used the same daily diary card used during the screening period to assess symptoms each day throughout the 12-week treatment period. Compliance to medication was assessed by return tablet count of not more than 10% of the prescribed medications. Patients were interviewed via telephone every week for assessment of symptoms and compliance, and were asked to return to hospital with diary cards every 1–2 weeks. The chief laryngeal complaint was considered to be improved after the start of the acid suppression therapy once the symptom score during the week since last interview had decreased by at least 50% compared with baseline. Patients were considered to have complete relief if the severity score of their chief laryngeal complaint was 0.

Sample size determination

The sample size was calculated as 32 patients per treatment group based on the outcome of improvement of chief laryngeal complaint at 12 weeks. This calculation assumes that 65% of patients with troublesome reflux symptoms report improvement of chief laryngeal complaint compared to 30% of patients without troublesome reflux symptoms, using the two-sample, two-tailed test with $\alpha = 0.05$, power $= 0.8$, and accounting for a 20% drop-out rate. If the prevalence of troublesome reflux symptoms in patients with chronic laryngitis was estimated to be 60%, we would be able to recruit at least 80 patients totally.[10,11]

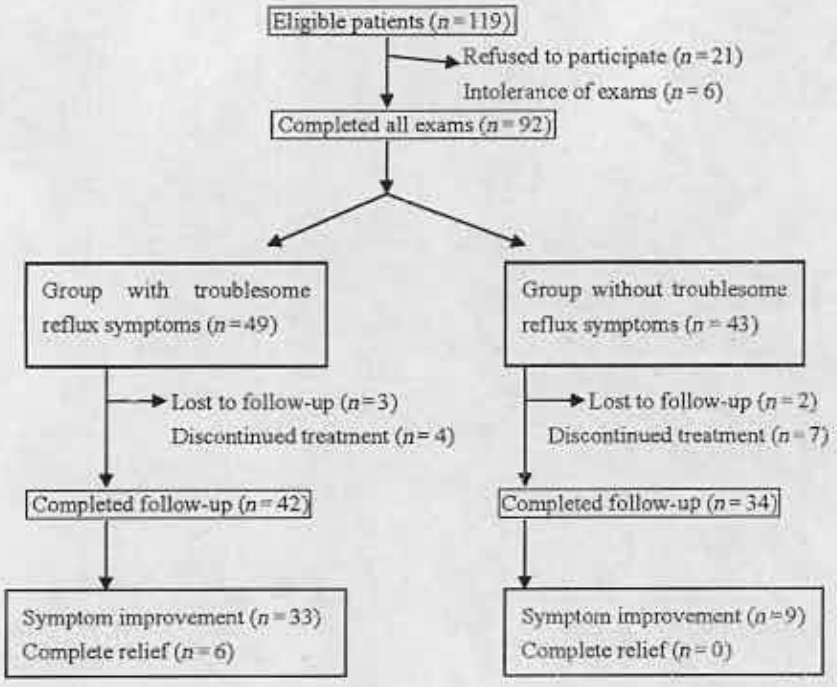

Figure 2 Summary of patient flow throughout study.

Statistical analysis

Distributions of sex, individual symptom, prevalence of GERD, and proportion of patients reporting improvement of chief laryngeal complaint were compared with Pearson's χ^2-test. Impedance and pH data were expressed as median and percentile values (25th, 75th and 95th percentiles). Comparisons of median values were made using the Mann–Whitney *U*-test. The Student's *t*-test was used to compare the distributions of age, body mass index (BMI) and the score of chief laryngeal complaint. The significance of the rate of the chief laryngeal complaint improvement was estimated with Kaplan–Meier analysis and log-rank test. If the chief laryngeal complaint at the completion of therapy had not decreased sufficiently, the Kaplan–Meier curve was described as "truncated". All *P*-values were two-tailed with the level of significance defined at 0.05. Data analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 389 patients with laryngeal symptoms were recruited from July 2007 to January 2009. One hundred and nineteen patients were found to have laryngoscopically proven laryngitis and were eligible for the study. Details of enrollment, treatment and follow up are shown in Figure 2. The dropout rate at the completion of therapy was 17.4% and was similar between the two groups. No serious adverse events occurred in either group.

Ninety-two patients agreed to participate in the study and completed all the exams. The most common chief laryngeal complaints were globus (29.6%), followed by throat clearing (27.6%), sore throat (15.3%), burning throat (15.3%), hoarseness of voice (11.2%) and throat dryness (1.0%). Baseline characteristics of each group are summarized in Table 1.

Seventy-six patients completed 12-week PPI therapy and 42 patients reported improvement of chief laryngeal complaint. Patients with troublesome reflux symptoms more often responded to acid suppression at 12 weeks (67.3% *vs* 20.9%, $P < 0.001$). Six patients with troublesome reflux symptoms but none of the patients without achieved complete relief of chief laryngeal complaint at 12 weeks. Figure 3 shows the improvement rates in the chief laryngeal complaint of these two groups. The improvement rates of the chief laryngeal complaint in patients with and without troublesome reflux symptoms 3 weeks after the start of acid suppression therapy were 40.8% and 14.0%, respectively. Patients with troublesome reflux symptoms therefore tended to improve more rapidly than those without (log-rank test, $P < 0.001$).

Twenty-two patients (23.9%) were diagnosed as having GERD with 19 patients having pathological acid reflux and five patients having erosive esophagitis. Patients defined as having GERD by objective exams also responded to acid suppression more often (72.7% *vs* 37.1%, $P = 0.003$) and more rapidly (log-rank test, $P = 0.02$, 54.5% *vs* 20.0% after the start of 3-week acid suppression therapy) than those without.

Discussion

This study is the first study to provide a thorough comparison between patients of chronic laryngitis with and without troublesome reflux symptoms using a bifurcated impedance-pH catheter in a large clinical sample. Data from this study indicate that these two groups of patients differ significantly from each other on most

Table 1 Comparison of baseline characteristics between patients with and without troublesome reflux symptoms

	Group with troublesome reflux symptoms ($n = 49$)	Group without troublesome reflux symptoms ($n = 43$)	P
General characteristics			
Age (years)	47.0 ± 13.2	37.2 ± 13.8	< 0.001**
BMI (Kg/m²)	22.9 ± 3.2	21.9 ± 3.4	0.13
Female (n, %)	28 (57.1%)	22 (51.2%)	0.85
Symptomatic characteristics			
Laryngitis history duration (median months)	20	18	0.91
Chief complaint score	10.0 ± 2.6	10.3 ± 2.4	0.60
Chief complaint (n, %)			
Throat pain	6 (12.2%)	9 (20.9%)	0.26
Burning throat	12 (24.5%)	1 (2.3%)	0.002*
Globus	13 (26.5%)	15 (34.9%)	0.39
Throat dryness	0	1 (2.3%)	0.47
Throat clearing	14 (28.5)	11 (25.6%)	0.75
Hoarse voice	4 (8.2)	6 (14.0%)	0.58
Endoscopic characteristics (n, %)			
EE	4 (8.2%)	1 (2.3%)	0.37
EE (Grade A)	2	1	0.99
EE (Grade B)	2	0	0.50
Characteristics of reflux profile			
Presence of PAR (n, %)	17 (34.7%)	2 (4.7%)	< 0.001**
Presence of LPR (n, %)	35 (71.4%)	10 (23.3%)	< 0.001**
Presence of acid LPR (n, %)	26 (53.1%)	6 (14.0%)	< 0.001**
GER (median [25th–75th–95th])			
GER reflux	59 (41, 68, 88)	52 (35, 66, 71)	0.10
Acid reflux	36 (28, 51, 62)	25 (16, 39, 49)	0.001*
Weakly acidic reflux	17 (9, 25, 45)	22 (16, 29, 51)	0.11
Weakly alkaline reflux	0 (0, 0, 3)	0 (0, 0, 6)	0.32
Mixed reflux	23 (15, 32, 41)	24 (13, 32, 41)	0.89
Liquid reflux	29 (20, 36, 46)	17 (12, 34, 53)	0.002*
Gas reflux	4 (1, 9, 13)	4 (2, 10, 15)	0.63
Proximal GER	11 (7, 19, 31)	7 (5, 9, 16)	< 0.001**
Proximal GER proportion (%)	20.0 (14.8, 35.6, 46.8)	15.6 (12.1, 21.2, 36.8)	0.003*
Bolus exposure (%)	1.1 (0.6, 1.5, 2.0)	0.8 (0.5, 1.1, 1.4)	< 0.001**
Proximal bolus exposure (%)	0.10 (0.06, 0.21, 0.38)	0.05 (0.03, 0.07, 0.13)	< 0.001**
Acid exposure (%)	2.2 (1.1, 4.4, 7.3)	1.2 (0.7, 1.7, 2.6)	< 0.001**
LPR (median [25th–75th–95th])			
LPR reflux	2 (0, 5, 6)	0 (0, 0, 6)	< 0.001**
Acid reflux	1 (0, 1, 3)	0 (0, 0, 1)	< 0.001**
Weakly acidic reflux	1 (0, 3, 5)	0 (0, 0, 5)	< 0.001**
LPR proportion (%)	4.1 (0, 7.9, 13.3)	0 (0, 0, 19)	< 0.001**
Bolus exposure (%)	0.003 (0, 0.009, 0.017)	0 (0, 0, 0.018)	< 0.001**
Acid exposure (%)	0.005 (0.003, 0.005, 0.018)	0.003 (0.002, 0.004, 0.005)	< 0.001**
Prevalence of GERD (n, %)*	19 (38.8%)	3 (7.0%)	< 0.001**

*$P < 0.05$; **$P < 0.001$.

BMI, body mass index; EE, erosive esophagitis; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; LPR, laryngopharyngeal reflux; PAR, pathological acid reflux.

analyzed items. They constitute two distinctive entities with different pathophysiological mechanisms and responses to acid suppression therapy.

As the larynx is an organ that is exposed to many exogenous irritants, the pathogenesis of chronic laryngitis is complicated and sometimes subtle. It is difficult to differentiate RLS from laryngitis of other causes. In our study, we questioned our patients painstakingly to exclude laryngitis with definite causes, and we are confident that the chronic laryngitis of patients is truly "idiopathic." In addition, we did not want to exclude patients who might benefit from PPI therapy with negative results in any one of the above tests as there is no "gold standard" for the diagnosis of RLS, so consecutive patients with laryngeal symptoms and laryngoscopically proven laryngitis were enrolled.

The current practice to identify GERD as the cause of RLS is to detect increased acid exposure by 24-h pH monitoring with dual

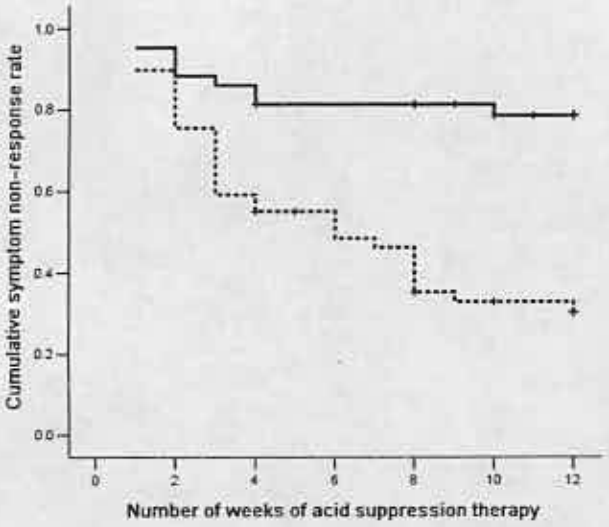

Figure 3 Kaplan–Meier analyses of response rates in patients with and without troublesome reflux symptoms. ⊓, without reflux; ⁝⁝, with reflux; +, without reflux-censored; +, with reflux-censored.

sensors, one placed at 5 cm above the upper margin of LES and the other around UES. However, laryngopharyngeal epithelium is far more susceptible to reflux-related injury than esophageal epithelium,[19] thus the non-acid LPR (pH > 4), which could not be detected by pH monitoring, may also lead to damage of laryngeal mucosa. Also, there is a high frequency of artifacts in pH monitoring due to the drying of pH sensor, the accumulation of food on sensor or the interruption of electrical continuity caused by loss of contact of the electrode with mucosa.[20–22] Therefore, in order to evaluate LPR accurately, it is essential to identify both acid and non-acid reflux around UES by 24-h MII-pH rather than pH monitoring. We used a new bifurcated impedance-pH catheter in order to allow esophageal pH electrode positioned 5 cm above the LES and laryngeal pH electrode positioned 0.5 cm above the UES simultaneously to assess the reflux profile of patients with chronic laryngitis. This type of bifurcated MII-pH catheter has been used in some studies to evaluate reflux in asymptomatic subjects.[23,24] However, it was used to evaluate reflux in consecutive chronic laryngitis patients in a large sample in our study for the first time.

Recent studies found that the prevalence of GERD in patients with chronic "idiopathic" laryngitis or globus was more than 60% based on symptoms and 20–40% based on pH monitoring and EGD.[10,11] We enrolled more patients with chronic "idiopathic" laryngitis and the results supported the above findings (56.5%, and 23.9%, respectively). However, a large proportion of patients with chronic laryngitis and troublesome reflux symptoms could not be diagnosed as GERD by 24-h monitoring and EGD. Reflux profile and response to acid suppression of these patients deserve further exploration. It would be simpler and more practical for doctors to evaluate patients according to symptoms rather than the diagnosis of GERD defined by objective exams in the daily clinical practice. We wished to replicate the situation in the generalists' office, where doctors would evaluate patients according to symptoms by the first impression. So patients in our study were classified by typical reflux symptoms rather than the diagnosis of GERD by objective exams.

Recent clinical trials and meta-analyses reported that a high-dose proton pump inhibitor is no more effective than placebo in producing improvement of extraesophageal symptoms.[3–5,8,9] However, these clinical trials excluded patients with frequent reflux symptoms because of ethical and safety issues and concerns. Our results suggest that perhaps few patients without troublesome reflux symptoms suffered RLS. It is not surprising the response to long-term and aggressive acid suppression of these patients was poor. Nowadays, the diagnosis of RLS more often depends on subjective judgment rather than objective signs or exams.[25,26] It is not surprising that some patients whose laryngeal symptoms were not caused by RLS would dilute the overall study population, resulting in reduced study power to detect a difference between PPI and placebo in randomized controlled trials. Our study could partly explain why PPI lack efficacy on suspected extraesophageal reflux symptoms in randomized controlled trials.

Our study has some limitations. First, it was not a placebo-controlled trial. It may have some placebo effects which would overestimate the efficacy of acid suppression on chronic laryngitis. However, the aim of our study was to compare the difference between patients with and without troublesome reflux symptoms. The comparative efficacy of PPI therapy between these two groups would be more important. Second, this study was conducted in a single centre and participants were mostly Cantonese, therefore selection and referral bias might exist and results may limit generalizability.

Chronic laryngitis is a disease in a heterogeneous condition. GERD may be just one of the causes or an aggravating factor. Patients with and without troublesome reflux symptoms may have different pathophysiological mechanisms and require different therapies. These could partly explain the discrepancy of response to acid suppression among patients with chronic laryngitis.

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