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Esophageal Reflux Episodes and Endoscopic Findings in Laryngopharyngeal Reflux Patients with Persistent Symptoms despite Acid Suppression Therapy

Sansak I[1], Leelakusolvong S[1], Charatcharoenwitthaya P[1], Prachayakul V[1], Pausawasdi N[1], Angsuwasrangsri T[2], Parichatikanond P[3], Tanwandee T[1], Chainuwatti S[1], Nimanong S[1], Pongprasobchai S[1], Manatsathit S[1], Kachintorn U[1], Udompanthurak S[4]

ABSTRACT

Background & Aim: Although micro-aspiration of gastric contents particularly acid reflux may be responsible for laryngopharyngeal reflux (LPR), some patients fail to respond to antisecretory therapy. The aims of this prospective study were to elucidate evidence of gastric reflux and its correlation with esophageal injury in nonresponder patients.

Methods: Forty-seven consecutive patients, who had signs and symptoms of chronic laryngitis and were refractory to at least 3-months empirical therapy with proton pump inhibitors, were enrolled. After cessation of acid-suppression medication for 2 weeks, all participants underwent upper gastrointestinal magnified narrow band endoscopy with esophageal biopsies followed by monitoring of gastroesophageal reflux episodes using multichannel intraluminal impedance (MII) 24-hour pH testing.

Results: Patients had a mean age of 48 ± 10 years; 81% were female; and mean body mass index was 22.3 ± 3.1 kg/m^2. At screening visit, 70% of patients reported symptoms of globus pharyngeus, 60% noted clearing throat, 60% had regurgitation, 53% reported heartburn and 40% developed hoarseness. Mean reflux symptom index (RSI) scores was 13 ± 7.9. Based on the MII-pH results, 409 liquid containing reflux events were recorded in 45 patients and 1,615 gas reflux events were detected in 28 patients. Among the cohorts with liquid reflux events, 11 patients (23%) were considered to have classic acid-reflux disease, 8 had "weakly acid" reflux episodes and 2 had "weakly alkaline" reflux episodes. Patients with classic acid-reflux disease were more often male (45% vs 11%, $p = 0.02$) and active alcoholic drinkers (27% vs 3%, $p = 0.04$) when compared to those without classic acid-reflux disease. Clinical characteristics including age, body mass index, history of smoking, laryngeal and gastroesophageal symptoms, the RSI scores, and duration of antisecretory therapy were similar between two groups. With white light endoscopy, erosive esophagitis were identified in only 2 patients documented to have classic acid-reflux disease on MII-pH testing. Subsequently, the magnified narrow-band imaging system was used to enhance visualization of esophageal mucosa. Non-erosive esophagitis was detected and confirmed by histology in 5 patients with classic acid-reflux disease, 3 patients with "weakly acid" reflux, 1 patient with "weakly alkaline" reflux, and 6 patients with gas reflux.

Conclusions: This study suggested that retrograde flow of gastric contents might be a cause of chronic laryngitic symptoms in some patients who do not respond to empirical antisecretory therapy. MII-pH monitoring and magnifying endoscopy might be helpful in further refinement of LPR treatment.

Key words : GERD, laryngopharyngeal reflux, MII -pH monitoring, magnifed NBI

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[1]Division of Gastroenterology, [2]Division of Otolaryngology, [3]Division of Pathology, [4]Clinical Epidemiology Unit, Office for Research and Development, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Address for Correspondence: *Somchai Leelakusolvong, M.D., Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder affecting 25% of the population[1]. The most common presenting symptoms of GERD are heartburn and regurgitation. In addition to heartburn and regurgitation, GERD may implicate in a variety of pulmonary symptoms and diseases such as asthma, bronchitis, micro-aspiration, and pulmonary fibrosis; ear, nose and throat symptoms and signs including hoarseness, cough, laryngitis, subglottic stenosis, and laryngeal cancer; and other extraesophageal findings such as non-cardiac chest pain, dental erosion, sinusitis, pharyngitis, and sleep apnea.

Laryngopharyngeal reflux (LPR) is the most common laryngeal manifestation of GERD, estimated 4-10% of patients presenting to an otolaryngology practice[2,3]. Patients have symptoms and/or findings related to GERD, hoarseness, vocal fatigue, chronic throat clearing, excessive throat mucus, chronic cough, dysphagia, and globus sensation.

However, there is conflicting evidence concerning the cause and effect relationship between LPR and GERD. LPR differs in many ways from GERD in that it is predominantly upright reflux, less associated with regurgitation and heartburn symptoms, less esophagitis comparing with GERD (10 % vs 40%) and low response rate to antireflux therapy[4,5]. The proposed hypotheses are laryngeal and esophageal mucosa may have different defensive mechanisms and laryngeal mucosa is susceptible to both acid and pepsin (activated at pH >5) or other types of refluxate.

Although micro-aspiration of gastric contents particularly acid reflux may be responsible for LPR, but patients with persistent symptoms on acid suppressive therapy are common, up to 50% of patients do not respond to aggressive acid suppression therapy[6]. Moreover recent meta-analysis showed that PPI therapy is no more effective than placebo in producing symptom relief in patients suspected of LPR[7]. It is not clear whether acid reflux pattern and esophageal mucosal sensitivity are involved in the development of LPR.

Nowadays, with an ambulatory multichannel intraluminal impedance (MII) and 24 hour-pH-monitoring test, the recognition of reflux events could be better achieved, it allows the demonstration of acid, weakly acid, non acid including type of acid reflux e.g. gas, liquid or mixed liquid/gas[8].

A narrow-band imaging (NBI) system is an endoscopic diagnostic tool for gastrointestinal tract. It enhances the endoscopic visualization of superficial neoplastic lesions and the microvascular architecture intrapapillary-capillary loops change. When it is combined with magnification of the image up to 115 times (magnified-NBI endoscopy), accuracy of the diagnosis is increased[9,10].

Because of the limited data in the PPI- non responders populations, we designed this prospective study to elucidate evidence of reflux content in nonresponder population by using the multichannel intraluminal impedance (MII) and 24 hour pH-monitoring test and magnified-NBI endoscopy. Our primary aim was to demonstrate the patterns and types of gastric reflux and the second aim was to demonstrate the correlation of the reflux content and esophageal injury.

MATERIALS AND METHODS

Subjects

Patients age between 18-80 years old with LPR which was diagnosed by otolaryngologist and failure to respond to antisecretory therapy (defined as the persistent LPR symptoms after 12 weeks of PPI therapy was given) were eligible for this study. Others causes of otolaryngologic symptoms were excluded. The LPR patients were excluded if they had contraindication to sedation, endoscopy, esophageal manometry or impedance/pH probe insertion, severe comorbidity (e.g. severe valvular heart disease, recent acute coronary event), sepsis, pregnancy, bleeding, bleeding tendency or not consent for interventions. The patients who had recent peptic ulcer bleeding and unable to stop PPI also were excluded. The study was conducted at Siriraj hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand from March to December 2009.

Interventions and Protocol

Enrolled patients stopped all acid-suppression medication for 2 weeks. A medical history, demographic data, duration and severity of GERD and LPR symptoms, duration of PPI and antacid therapy, history of smoking and alcohol consumption were collected. All patients were asked to complete the reflux questionnaire for reflux symptoms. We used the 9-item reflux symptom index (RSI) as described by Belafsky *et al*[11]. The patients who had no symptoms persistence within 1 month before the study (RSI = 0) were excluded. Each patient underwent upper gas-

trointestinal magnified NBI endoscopy with esophageal mucosal biopsy, esophageal manometry and impedance/24-hour ambulatory esophageal pH monitoring test. All these studies were performed within 7 days of each other. All investigators (endoscopists, pathologist, tracing result interpreter) were blinded from other testing results.

Esophagoscopy

Each individual underwent upper gastrointestinal endoscopy under appropriate sedation (intravenous midazolam and propofol) and local pharyngeal anesthesia. Magnified NBI endoscope (Olympus GIF-Q160Z 240) videogastroscope was used for all patients. Erosive esophagitis was noted, and the Los Angeles classification system was used to establish the degree of erosion present. Hiatus hernia was diagnosed if more than 2 cm of gastric mucosa was detected above the diaphragm on endoscopy. Vascular architecture abnormality detected by magnified-NBI was classified into 4 types according to degree of change in intrapapillary capillary loop (IPCL) applied from the studies of Inoue *et al*[12]. Changes include dilatation, tortuosity, and/or caliber change of individual IPCL, or multiple IPCLs of various shapes. Type I is a normal IPCL pattern, type II is minimal dilatation and elongation of IPCL which corresponded to esophagitis. In type III, minimal changes in IPCL are observed; types III and IV corresponded to mild and severe dysplasia, as Figure 1[12,13].

The endoscopic findings were recorded with video record files and the pictures (Olympus VDO recording system). Other abnormalities found were also recorded. Two blinded investigators reviewed each endoscopic findings and video recorded files with a separate endoscopic score. If the score was different, then discussion occurred. The 3rd expertise endoscopist for assessment was necessary if there was disagreement.

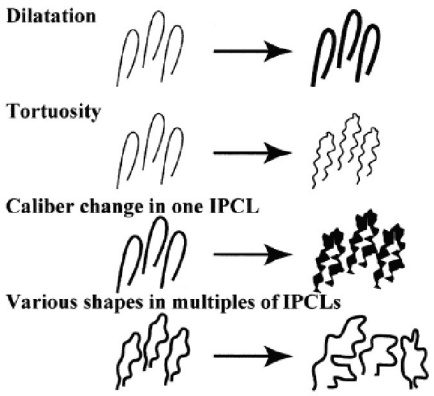

Figure 1. Vascular architecture abnormality detected by magnified-NBI[12]

Histopathological Evaluation

Esophageal mucosal tissues were randomly retrieved from upper esophagus (2 cm distal to upper esophageal sphincter (UES), lower esophagus (2 cm proximal to esophagogastric junction (EGJ) and middle esophagus (middle part between upper and lower part) at the time of endoscopy. The tissues were collected separately and fixed with formalin. Tissue was stained with hematoxylin and eosin and evaluated by single pathologist. The findings were reported separately for each part of esophagus.

Esophageal Manometry and Ambulatory Impedance 24 Hours pH-monitoring Test

All patients were asked to stop all prokinetic drugs for at least 3 days before testing. On outpatient basis, all presented to perform combined MII-pH testing after at least 6 hours of fasting. The combined MII-pH probe was placed in reference to the manometrically located proximal border of the lower esophageal sphincter (LES). On completion of the manometry, a 2.1 mm MII-pH catheter was passed transnasally and the esophageal pH sensor was positioned 5 cm above the LES. The configuration of the catheter allowed monitoring changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm above the LES. In addition, pH was monitored at 5 cm above the LES. Patients then underwent 24 hour MII-pH monitoring and diaries were provided for patients to record symptoms during the study period. Data from the impedance channels and pH electrodes were sampled at a frequency of 50 Hz and stored on a portable data recorder (intraluminal impedance and 24 hour-pH monitoring (Ohmega) impedance/pH electrode, 6 impedance and 1 pH channel, Medical Measurement Systems, USA). At the end of the 24 hour recording period, data were transferred and analyzed using dedicated software (Virtual instructor Program Analysis; Medical Measurement Systems, USA). Tracings were reviewed and timing of meals, changes in body position, and the time of symptoms recorded were compared with the information written in the diaries. Meal periods were marked and excluded from the analysis.

Twenty-four-hour pH data collected included the

following; (1) the total percentage of time pH <4, (2) the DeMeester score, (3) percentage of proximal extent in upright and supine position, (4) the number of reflux episodes, (5) acid reflux (decrease of pH to <4 for at least 5 seconds) and (6) weakly acid reflux (decrease in pH of at least 1 log unit for at least 5 seconds without a decrease in pH to <4).

Impedance data collected included the following: (1) liquid reflux events, defined as a retrograde decrease of impedance of at least 50% beginning at the lower esophageal sphincter and involving at least 2 other proximal channels; (2) gas reflux events (defined as a simultaneous rapid increase in impedance (5000-10,000 Ohm) noted in at least 2 distal impedance channels); (3) mixed reflux events, defined as gas reflux coming immediately before or immediately after liquid reflux; and (4) nonacid reflux events, defined as an impedance reflux event with a less than 1 log unit of pH change during the episode[9].

The study was approved by the Siriraj Ethics Committee. All patients were informed in detail about all steps of the study and written consent was provided by all patients before the study.

Statistical Analysis

Data were analyzed using the SPSS 13.0 Basic software package of statistical programs. The patterns and types of gastric reflux were based on an observational data, χ^2 test was used for comparison between classic and non classic reflux disease groups. Statistical significance was established at $p \leq 0.05$.

Results

Of the 47 patients enrolled in our study, 39 women and 8 men, with an average age of 48 years (range 18-64 years) and mean body mass index was 22.3 ± 3.1 kg/m^2 who had diagnosis of LPR by otolaryngologist for average of 26.5 months (range 3- 84 months). Other potential causes of related signs and symptoms were excluded. All patients were treated with high dose proton pump inhibitors twice daily for at least 3 months (average 27 months, range 3-84 months), H_2-receptor antagonist (H_2RA) was combined in 25% of patients, all without improvement of LPR symptoms. At the screening visit, 70% of patients reported symptoms of globus pharyngeus, 60% noted clearing throat, 60% had regurgitation, 53% reported heartburn and 40% developed hoarseness. Mean reflux symptom index (RSI) scores was 13 ± 7.9. Two and 4 of 47 patients had a history of smoking and alcohol consumption respectively. Esophageal manometry was performed in all patients and we found nut-cracker pattern in one patient who suffered from globus symptom for 12

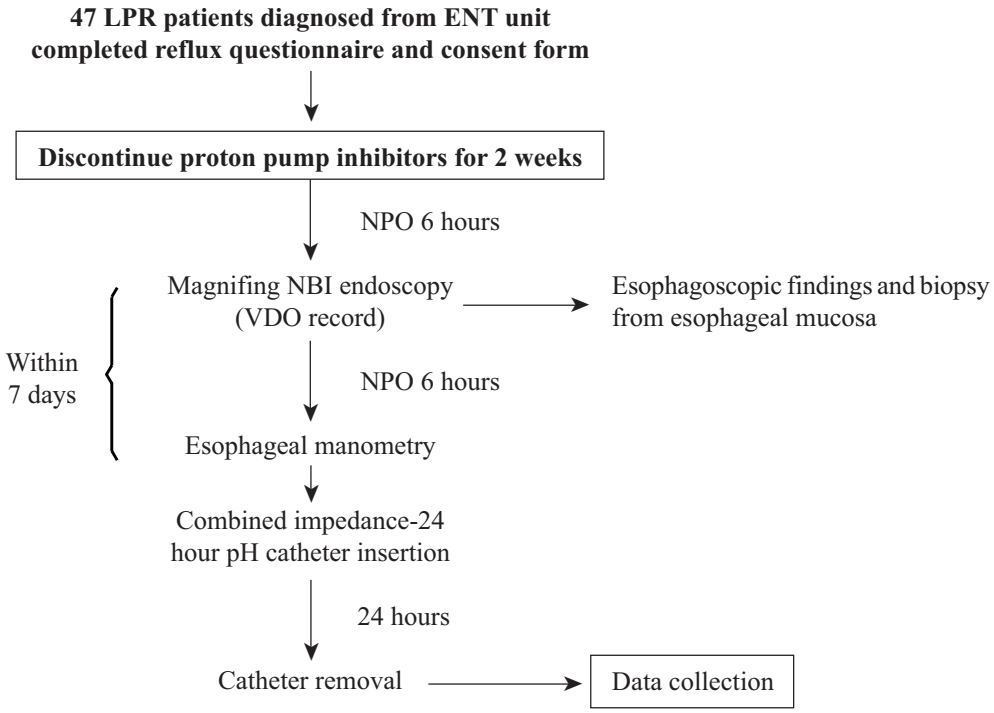

Figure 2. Study Scheme

months. She did not have dysphagia. Eleven (23.4%) of 47 patients had pathological acid reflux (positive monitoring test pH < 4). The average total reflux number was 31.57 ± 29.93 times. (Table 1)

Based on the MII-pH results, 21.3% of patients had acid reflux, 21.3% had weakly acid reflux and nonacid reflux was found in 2% of patients. Most of the patients had pure abnormal gas refluxates (46.8%), 6.4% had abnormal mixed refluxates, 21.3% had abnormal mixed and gas refluxates, 2.1% had abnormal liquid and mixed refluxates, 4.3% had all type of refluxates (liquid, mixed and gas) and no pure abnormal liquid refluxate was detected in our study. (Table 2) Among this cohort, 409 liquid containing reflux events were recorded in 45 patients and 1,615 gas reflux events were detected in 28 patients. Among the cohorts with liquid reflux events, 11 patients (23%) were considered to have classic acid-reflux disease, 8 patients had "weakly acid" reflux episodes and 2 patients had "weakly alkaline (non acid)" reflux episodes. Patients with classic acid-reflux disease were more often male (45% vs 11%, $p = 0.02$) and active alcohol drinkers (27% vs 3%, $p = 0.04$) when compared to those without classic acid-reflux disease. Clinical characteristics including age, body mass index, history of smoking, laryngeal and gastroesophageal symptoms,

Table 1. Demographic data and characteristics of patients

Characters	Total (N = 47)
Age (years): mean (SD)	48 (10)
Sex (female): number (%)	39 (81)
Body mass index (km/m^2) : mean (SD)	22.3 (3.1)
Cigarette smoking status (%)	2 (4.3)
Alcohol consumption (%)	4 (8.5)
Globus (%)	33 (70)
Hoarseness of voice or voice change (%)	19 (40)
Clearing throat /secretion sensation (%)	28 (60)
Heartburn (%)	25 (53)
Regurgitation (%)	28 (60)
Duration of symptom (month): range (median)	3-84 (26.5)
Duration of PPI treatment (months): range (median)	3-84 (26.7)
Reflux symptom index: mean (SD)	13 (7.9)

Table 2. Acid exposure and refluxate type

	Total (N = 47)
Pathological acid reflux (%)	11 (23.4)
Total reflux number	31.57 ± 29.93
% Proximal extent at upright position	11.13 ± 15.26
% Proximal extent at supine position	5.59 ± 15.31
Acid reflux (%)	10 (21.3)
Weakly acid reflux (%)	10 (21.3)
Non-acid reflux (%)	1 (2.1)
Liquid reflux (%)	0
Mixed type reflux (%)	3 (6.4)
Gas reflux (%)	22 (46.8)
Liquid and mixed reflux (%)	0
Liquid and gas reflux (%)	0
Mixed and gas reflux (%)	10 (21.3)
Liquid and gas and mixed reflux (%)	2 (4.3)

Table 3. Clinical characteristics between the classic and non classic reflux disease

Characteristics	Classic acid reflux disease (N = 11)	Non classic reflux disease (N = 36)	*p*-value
Age (years ± SD)	50 ± 7	47 ± 11	0.37
Sex : female	6	32	0.02
Body mass index (km/m^2)	23.92 ± 3.04	21.81 ± 2.93	0.61
Cigarette smoking status	1	1	0.42
Alcohol consumption	3	1	0.04
Globus	6	27	0.26
Hoarseness of voice or voice change	5	14	0.74
Clearing throat /secretion sensation	6	22	0.74
Heartburn	7	18	0.51
Regurgitation	7	21	1.00
Duration of symptom (months)	23.91 ± 20.91	27.31 ± 20.40	0.84
Duration of PPI treatment (months)	23.73 ± 20.97	27.64 ± 20.44	0.68
Reflux symptom index:mean	13.73 ± 7.13	12.78 ± 8.26	0.59

Table 4. Esophagoscopic findings

Findings (%)	Total (N = 47)
Esophagitis by white light endoscopy	3 (6)
Inlet patch	15 (32)
Hiatal hernia	1 (2)
IPCL change by Magnified-Zoom NBI endoscopy	30 (64)
Abnormal vascular pattern	
- IPCL change of lower part of esophagus	11 (23)
- IPCL change of lower and middle part of esophagus	7 (15)
- IPCL change of lower, middle and upper part of esophagus	10 (21)
- Focal area of IPCL change	2 (4)

the RSI scores, and duration of antisecretory therapy were similar between the two groups (Table 3).

During white light endoscopy, erosive esophagitis was found in 3 of all study patients which only 2 patients documented to have classic acid-reflux disease on MII-pH testing. Hiatal hernia was found in one patient. Interestingly, inlet patch was found in 15 of 47 patients.

When the narrow-band magnified imaging system was used to enhance visualization of esophageal mucosa, 30/47 (64%) of patients had abnormal vascular pattern defined by intrapapillary-capillary loop elongation, widening or distortion. These abnormalities were localized in the lower part of esophagus in 11 patients (23.4%), lower and middle part esophagus in 7 patients (14.9%), in all part of esophagus in 10 patients (21.3%) and 2 patients (4.3%) had scatter areas of abnormal vascular pattern (Table 4). Among who had abnormal findings, 15 patients had reflux symptom index > 13, 8 patients had classical acid reflux, 6 patients had weakly acid reflux and 16 patients had no reflux detected by MII impedance monitoring test. For refluxate type, 12 patients had pure gas refluxates, 8 patients had mixed and gas refluxates, 1 patient had liquid and mixed refluxates, and 2 patients had all type of refluxates. The non-erosive esophagitis was confirmed by histology in 5 patients with classic acid-reflux disease, 3 patients with "weakly acid" reflux, 1 patient with "non acid" reflux, and 6 patients with gas reflux.

DISCUSSION

Although the pathogenesis of LPR is not yet well established, 2 mechanisms have been proposed i.e. LPR is mediated by a reaction originating from an acid-sensitive esophagus, and a consequence of direct acid injury by the acid gastric content, making LPR a category of GERD. As previously mentioned, LPR is different from GERD in both its manifestation and response to treatment. This leads us to believe that there could be some other factors which can cause the difference, for example, the sensitivity of laryngeal mucosa to destruction of acid reflux as in GERD but the former is more sensitive, or acid gastric content as previously studied in NERD is found to have non-acid flux as one of the major mechanisms, which causes persistent symptoms in patients with NERD. From that study, it is shown that 66.7% of NERD patients, without PPI therapy, had abnormal esophageal acid exposure[14], there could be no relation to the occurrence of reflux which could explain why only 50% of the patients responded to the PPI therapy and required large dosages for a long period of time, making the treatment a controversy.

At present, it is found that combined multichannel intraluminal impedance (MII) and 24 hour-pH-monitoring test is more effective in detecting any irregularity of reflux than the traditional pH monitoring test and thus widely implemented in NERD studies. However, available data and studies relating to abnormal acid exposure are relatively limited. Our study is regarded as first of its kind in LPR patients who do not respond to the PPI treatment. We found that the patients have acid reflux 21%, weakly acid reflux 1% and non acid reflux 2%, whose irregularity can be detected better than pH-monitoring test (44.7% vs 24.3%). Moreover, we found that the patients had pure abnormal gas refluxates (46.8%), 6.4% had abnormal mixed refluxates, 21.3% had abnormal mixed and gas refluxates, 2.1% had abnormal liquid and mixed refluxates, 4.3% had all type of refluxates (liquid,

mixed and gas). This illustrates that there is evidence of retrograde gastric content which could possibly be acid, weakly acid, non-acid gas liquid or mixed type, in our study group.

From Magnified Zoom NBI endoscopy, we found that 64% of the patients had abnormal vascular pattern which implies mucosal injury. Results from conventional white light endoscopy revealed 6% of inflammation. Moreover, abnormality found localized at the lower part of esophagus to be 23% and extended upward to upper part of esophagus 21%, supporting mucosal injury in the patient group and this could be related to gastric reflux content. We also found that the patients have inlet patch as many as 32%.

Our study revealed that there were more male patients with classic acid-reflux disease than female (45% vs 11%, $p = 0.02$) and active alcoholic drinkers (27% vs 3%, $p = 0.04$) when compared to those without classic acid-reflux disease. Clinical characteristics including age, body mass index, history of smoking, laryngeal and gastroesophageal symptoms, the RSI scores, and duration of antisecretory therapy were similar between two groups.

As previously mentioned, this study is the first of its kind in investigating non PPI responder patients which is still practically challenging. However, as LPR patients amounted to only 50%, this could mean that the sample does not represent the majority of LPR patients. Moreover, diagnostic criteria regarding LPR in our study is not well defined as it is a known fact that the present criteria yet well established, whether they be reflux index score, or reflux finding score, as their specificity is not well defined, which could be the limitation of the present study. In our study, we then enrolled only patients who were diagnosed by experts in LPR and reconfirm the diagnosis before participation. Moreover, vascular abnormality from magnified NBI endoscopy has not yet been studied comparatively in normal population before. Therefore, it is not possible to conclude if abnormality found by NBI is related to LPR. However, we found that the method enabled us to discover other abnormality such as inlet patch more effectively than white light endoscopy. It remains to be investigated if the abnormality does indeed relate to LPR.

In conclusion, this study suggests that retrograde flow of gastric contents may be a cause of chronic laryngitic symptoms in some patients who do not respond to empirical antisecretory therapy. MII-pH monitoring and magnifying endoscopy might be helpful in further refinement of LPR treatment.

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