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Pharyngeal reflux episodes in patients with suspected laryngopharyngeal reflux versus healthy subjects: a prospective cohort study

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Abstract

Purpose This study aimed to analyze pharyngeal reflux episodes in patients with suspected LPR versus healthy subjects using 24-h MII-pH monitoring.

Methods One hundred twenty-one patients who visited our clinic with a chief complaint of LPR-related symptoms and underwent 24-h MII-pH monitoring were enrolled prospectively. Also, 27 healthy subjects were enrolled and underwent 24-h MII-pH monitoring during the same period. We analyzed sensitivity, specificity, and accuracy comprehensively to determine appropriate cut-off values of pharyngeal reflux episodes in 24-h MII-pH monitoring to diagnose patients with LPR.

Results Twenty-nine of 121 patients with suspected LPR showed no pharyngeal reflux episodes, while 92 showed more than one pharyngeal reflux event. In contrast, the 22 healthy subjects showed no pharyngeal reflux episodes, three showed one reflux event, and two showed two reflux events. A cut-off value of ≥ 1 showed best accuracy reflected by combined sensitivity and specificity values, while ≥ 2 demonstrated better specificity with slight loss of sensitivity and slightly lower overall accuracy, suggesting cut-off value of ≥ 1 pharyngeal reflux episodes is a good clinical indicator.

Conclusion A cut-off value of ≥ 1 in pharyngeal reflux episodes on 24-h MII-pH monitoring in patients with suspected LPR might be an acceptable diagnostic tool for LPR.

Keywords Laryngopharyngeal reflux · Multichannel intraluminal impedance (MII)-pH · Pharyngeal reflux episodes · Diagnostic criteria · Cut-off value

Introduction

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissue related to direct and indirect effects of gastroduodenal content reflux, which induces morphological changes in the upper aerodigestive tract [1]. The diagnosis of LPR has traditionally been made based on the presence of laryngeal symptoms and laryngoscopic findings. However, laryngeal symptoms and laryngoscopic findings cannot be used alone to diagnose LPR because of their low sensitivity and specificity [2]. Laryngeal symptoms can occur in the absence of conclusive laryngeal findings and be nonspecific [3].

The ambulatory 24-h double-probe pH monitoring test, which was developed to diagnose gastroesophageal reflux disease (GERD), may be considered the gold standard for the diagnosis of LPR [4]. However, this approach does not detect nonacid reflux episodes in the esophagus or

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hypopharyngeal cavity. Multichannel intraluminal impedance (MII)-pH monitoring compared to other diagnostic tools is the most reliable means to precisely diagnose acid, nonacid, or mixed reflux [1]. However, there are no standard diagnostic criteria for interpreting MII-pH findings. Various parameters such as total acid exposure time, DeMeester score, and acid reflux episodes have been used to diagnose LPR [5–9]. However, these parameters might not diagnose nonacid LPR. A pharyngeal reflux episode detected by MII-pH can reflect episode numbers of all reflux types in patients with LPR, but diagnostic cut-off values of pharyngeal reflux episodes differ among journals [4, 10]. In addition, diverse MII-pH catheter models are used. For example, a specialized bifurcated impedance catheter was used in one study [11].

This study aimed to analyze pharyngeal reflux episodes in patients with suspected LPR and healthy subjects using 24-h non-bifurcated hypopharyngeal-esophageal MII-pH monitoring and determine the cut-off value of pharyngeal reflux episodes to differentiate patients with LPR from normal subjects.

Subjects and methods

Subjects and study design

Patients who visited our clinic with a chief complaint of LPR-related symptoms were studied prospectively from September 2014 to September 2019. LPR-related symptoms included globus sensation, hoarseness, troublesome cough, frequent throat clearing, throat pain, odynophagia, halitosis, regurgitations, heartburn and postnasal drip in this study. All patients completed the reflux symptom index (RSI) questionnaire; highly validated survey with nine questions to assess the level of severity of LPR [12]. Patients were examined with a nasopharyngolaryngoscope by an ENT specialist in a routine laryngeal examination, then LPR-related findings such as subglottic edema, ventricular obliteration, posterior commissure hypertrophy, and thick endolaryngeal mucous were noted.

Inclusion criterion was the ability to safely tolerate unsedated transnasal endoscopy. Exclusion criteria included age < 19 and > 75 years, proton pump inhibitor (PPI) intake within 2 weeks, H_2 blocker or antacid intake within 1 week, history of head and neck malignancy, radiation therapy to head and neck, and current pregnancy. A total of 121 subjects who matched the criteria above were regarded to have suspected LPR [13] and underwent 24-h MII-pH monitoring.

Also, healthy subjects without LPR-related symptoms were recruited through community advertising during the same period. Healthy subjects were also examined with a nasopharyngolaryngoscope to exclude subjects showing laryngeal pathologic findings such as granuloma, laryngitis or laryngeal mucosal lesion. The inclusion and exclusion criteria were the same as described above. Also, subjects who had any past history of GERD or LPR symptoms were excluded. Finally, 24-h MII-pH monitoring was performed in 27 healthy subjects who met the criteria above.

The authors obtained approval from the institutional review board (IRB) before the start of the study (IRB No. 2018–06-046). And, all subjects provided written informed consent before being included in this study.

Twenty-four-hour multichannel intraluminal impedance-pH monitoring

A single-use MII-pH probe was inserted by two ENT doctors. The dual-channel MII-pH catheter models (ZAI-BL-54, 55,56, ComforTEC Z/PH single-use 2.3-mm-diameter probe; Sandhill Scientific, Inc., WI, USA) were used based on the patient's esophageal length and the correct model was selected. This catheter incorporated six impedance segments (z6, z5, z4, z3, z2, z1, respectively positioned at 5, 7, 12, 14, 26, 27 cm above the lower esophageal sphincter) and two pH measuring electrodes, which were monitored at the hypopharynx (proximal pH) and esophagus (distal pH). After insertion of the nasopharyngolaryngoscope into the nasal cavity for direct visualization of the probe, the dual-channel MII-pH catheter was inserted transnasally into the opposite side of the nose. A blue visualization band 1 cm below the proximal pH sensor was placed at the proximal edge of the upper esophageal sphincter (UES) while subjects were performing Valsalva maneuvers [4]. The probe was attached to an external ambulatory recording device (ZepHr Compact Flash Card and Recorder, Sandhill Scientific Inc.) for 24 h.

To reduce artifacts related to swallow and air trapping, all subjects were instructed to maintain their usual meals. They were instructed to avoid alcohol, caffeine, proton pump inhibitor drugs, and other potentially interfering substances. They were also instructed to record the beginning and ending times of meals, and a recumbent position state by pressing the button on the pH data logger. The inserted probe was removed at least 23 h, and the MII-pH data were downloaded. Recorded data were manually analyzed by one expert using a software program (BioView Analysis, Sandhill Scientific, Inc., Highlands Ranch, CO, USA). The meal periods were excluded from the analysis.

Test interpretation

A liquid reflux episode was defined as a retrograde 50% fall in impedance from the mean baseline impedance between the two electrode pairs. The mean was calculated from baseline impedance values measured 5 s prior to the decrease. A gas reflux episode was defined as a rapid (3 kΩ/sec) increase

in any two consecutive impedance sites with one site having an absolute value > 7000 Ω in the absence of swallowing. A mixed liquid–gas reflux episode was defined as gas reflux occurring immediately before or during a liquid reflux episode. A pharyngeal reflux episode was defined as when the refluxate (liquid + gas + mixed) reached pharynx channels z1 or z2 of impedance, and classified as acidic if the pH decreased below 4 and as nonacidic if the pH remained above 4 during the episode [11, 14].

Statistical analysis

Statistical analyses were performed using R software package (http://www.r-project.org). The differences in pharyngeal reflux episodes on 24-h MII-pH monitoring between patients with suspected LPR and healthy subjects were evaluated using the chi-square test. Values of $p < 0.05$ were considered statistically significant. We calculated sensitivity, specificity, and accuracy values according to each cut-off value. Sensitivity, specificity, and accuracy described the proportion of actual positives that were correctly identified, the proportion of actual negatives that are correctly identified, and the proportion of actual results that are correctly identified, respectively. Receiver operating characteristic (ROC) curve was schematically depicted to show the value of sensitivity plus specificity for each cut-off value of pharyngeal reflux episodes on 24-h MII-pH monitoring.

Results

One hundred twenty-one patients with suspected LPR and 27 healthy subjects were evaluated using 24-h MII-pH monitoring. Patient demographics are summarized in Table 1. Forty-six male and 75 female patients were included in the suspected LPR group, while 6 male and 21 female participants were included in the healthy subjects group.

Pharyngeal reflux episodes on 24-h MII-pH monitoring are summarized in Table 2. Twenty-nine of 121 patients with suspected LPR showed no pharyngeal reflux episodes, while 92 showed more than one pharyngeal reflux event (pharyngeal reflux events, 1–35). On the other hand, 22 healthy subjects showed no pharyngeal reflux episodes. Only three healthy subjects showed one reflux event, while two subjects showed two reflux events.

Tables 3 and 4 show the number of subjects in each group scoring above and below a cut-off value of ≥ 1 or ≥ 2 in pharyngeal reflux episodes on 24-h MII-pH monitoring. Chi-square test regarding the correlation of a cut-off value of ≥ 1 or ≥ 2 for pharyngeal reflux episodes and risk of suspected LPR in total subjects showed a significant correlation ($p < 0.001$, < 0.001, respectively).

Sensitivity, specificity, and accuracy were derived from each cut-off value (≥ 1, ≥ 2, ≥ 3, ≥ 4) of pharyngeal reflux episodes and are described in Table 5. Cut-off values ≥ 5 showed very low sensitivity and are not described. ROC curve was schematically depicted in Fig. 1 to show each

Table 1 Participant demographics

Variable	Patients with suspected LPR ($n = 121$)	Healthy subjects ($n = 27$)
Age	53.83 ± 12.61†	43.56 ± 14.05†
Sex (male:female)	46:75	6:21
Diabetes mellitus	7 (5.79%)	0
Hypertension	36 (29.75%)	0
Smoking	22 (18.18%)	5 (18.52%)
Alcohol	34 (28.10%)	8 (29.63%)
Coffee	53 (43.80%)	23 (85.19%)
RSI	13.89 ± 5.36†	1.56 ± 2.55†

LPR laryngopharyngeal reflux, *RSI* reflux symptom index

†Values of age was presented as Mean ± standard deviation

Table 2 Number of subjects in each group by number of reflux events on 24-h MII-pH monitoring

Reflux events	Group		Total
	Patients with suspected LPR ($n = 121$)	Healthy subjects ($n = 27$)	
0	29	22	51
1	10	3	13
2	19	2	21
3	15	0	15
≥ 4	48	0	48

MII multichannel intraluminal impedance, *LPR* laryngopharyngeal reflux

Table 3 Number of subjects in each group scoring a cut-off value of 1 for pharyngeal reflux episodes during 24-h MII-pH monitoring

Cut-off value (pharyngeal reflux episodes)	Group		Total ($n = 148$)
	Patients with suspected LPR ($n = 121$)	Healthy subjects ($n = 27$)	
≥ 1	92	5	97
< 1	29	22	51
p-value	< 0.001*		

MII multichannel intraluminal impedance, *LPR* laryngopharyngeal reflux

*$p < 0.001$, Results of chi-square test regarding the correlation of a cut-off value of 1 for pharyngeal reflux episodes and risk of suspected LPR in total subjects

Table 4 Number of subjects in each group scoring a cut-off value of 2 for pharyngeal reflux episodes on 24-h MII-pH monitoring

Cut-off value (pharyngeal reflux episodes)	Group		Total ($n=148$)
	Patients with suspected LPR ($n=121$)	Healthy subjects ($n=27$)	
≥ 2	82	2	84
<2	39	25	64
p-value	<0.001*		

MII multichannel intraluminal impedance, *LPR* laryngopharyngeal reflux

*$p<0.001$, Results of chi-square test regarding the correlation of a cut-off value of 2 for pharyngeal reflux episodes and risk of suspected LPR in total subjects

Table 5 Sensitivity, specificity, and accuracy for each cut-off value of pharyngeal reflux events during 24-h MII-pH monitoring

Cut-off value	Sensitivity	Specificity	Accuracy
≥ 1	0.760	0.815	0.770
≥ 2	0.678	0.926	0.723
≥ 3	0.521	1.000	0.608
≥ 4	0.397	1.000	0.507

MII multichannel intraluminal impedance

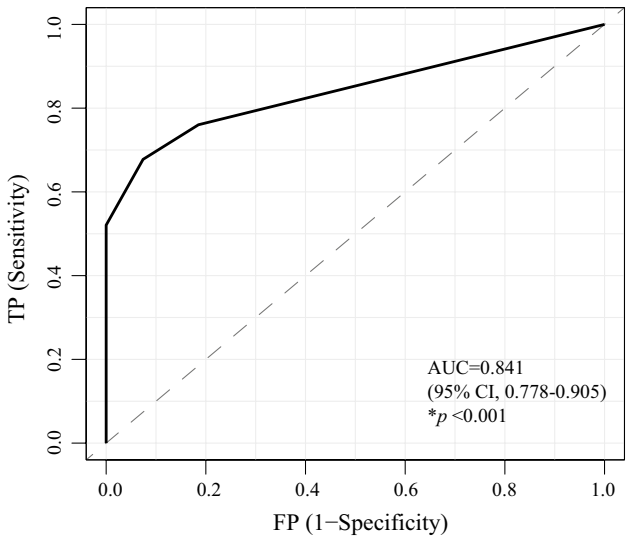

Fig. 1 ROC curve analysis showing each cut-off value of pharyngeal reflux episodes for predicting LPR. *LPR* laryngopharyngeal reflux, *ROC* receiver operating characteristic, *TP* true positive, *FP* false positive, *AUC* area under the ROC curve, *CI* confidence interval

cut-off value of pharyngeal reflux episodes for predicting LPR. The area under the ROC curve (AUC) was 0.841 (95% confidence interval [CI], 0.778–0.905, $p<0.001$), indicating good discriminatory ability [15]. A cut-off value of ≥ 1 in pharyngeal reflux episodes showed high sensitivity (0.760), specificity (0.815), and the highest accuracy (0.770) in various cut-off values. On the other hand, a cut-off value of ≥ 2 showed slightly better specificity (0.926), but lower sensitivity (0.678) and accuracy (0.723).

Discussion

LPR-related symptoms are nonspecific and may be associated with allergy, smoking, environment, toxic inhalant, infection, or vocal abuse [16]. To prevent the overdiagnosis of LPR resulting from these characteristics, some diagnostic tools have been established and developed. Diagnosis with combined laryngeal symptoms and laryngoscopic findings had been used for many years with empirical PPI therapy [1]. But, symptomatic or laryngeal finding tools are not so reliable than previously presumed for many reasons [17–19].

MII-pH monitoring is a more objective diagnostic tool than symptomatic or laryngeal finding tools and may have been considered the gold standard for diagnosing LPR by many otolaryngologists [10]. MII-pH monitoring is also the most reliable means to precisely diagnose acid, nonacid, or mixed reflux [1]. However, many otolaryngologists do not use MII-pH because of patient inconvenience and lack of tolerance, unclear indications, and a perceived lack of benefit of this approach for LPR management [20]. Above all, MII-pH monitoring includes various parameters, but there is no standard for interpreting these parameters. Unlike other parameters of MII-pH monitoring, pharyngeal reflux episodes can reflect all types of reflux including acid, nonacid, liquid, and gas. However, there are few studies on cut-off values of pharyngeal reflux episodes to diagnose patients with LPR. In one study on normative data for pharyngeal reflux episodes, reflux episodes were extremely rare in subjects without LPR-related symptoms [11]. However, the number of pharyngeal reflux episodes might vary from day to day, resulting in no reflux episodes during the 24-h testing period [21]. Asymptomatic subjects could show pharyngeal reflux events during the 24-h MII-pH monitoring period [11]. Thus, here we aimed to identify appropriate cut-off values of pharyngeal reflux episodes during 24-h MII-pH monitoring by comparing patients with suspected LPR with healthy subjects.

Although a cut-off value of ≥ 2 pharyngeal reflux episodes showed the highest value (1.604) of sensitivity plus specificity in various cut-off values, a cut-off value of ≥ 1 pharyngeal reflux episodes might be appropriate because of the highest accuracy and balanced high sensitivity and specificity compared to other cut-off values. A previous study stated that patients with one or more laryngopharyngeal reflux events in bifurcated hypopharyngeal MII should be considered abnormal [11]. Thus, we expected that 1 pharyngeal reflux episode

during 24-h MII-pH monitoring might be the proper cut-off value to diagnose LPR. Compared to a previous study that excluded subjects complaining of typical LPR symptoms and showing no reflux events on MII, we analyzed them together to avoid selection error.

There are some limitations to our study. First, there is no absolute gold standard for LPR diagnosis, thus simple ROC analysis could not be done in this study. The ROC curve of pharyngeal reflux episodes was only schematically depicted using Table 5 to show the value of sensitivity plus specificity for each cut-off value. Instead, we analyzed sensitivity, specificity, and accuracy comprehensively to determine the appropriate cut-off value to predict patients with suspected LPR. Second, we used a single branch catheter, unlike other studies using bifurcated catheter [11, 22]. All patients do not have the same heights of the esophagus, so the probe may not be correctly located in the pharynx and distal esophagus, simultaneously. However, we focused on measuring reflux episodes at the hypopharynx, not distal esophagus, because most patients with suspected LPR did not complain of GERD symptoms such as heartburn, regurgitation, etc. We used nasopharyngolaryngoscope for direct visualization and exact location of pharynx channel z1 and z2 of impedance. In addition, we selected a single branch catheter because most patients commonly complain of less discomfort when applied with a single branch catheter than bifurcated catheter. Third, many patients with suspected LPR showed no pharyngeal reflux episodes in 24-h MII-pH monitoring. LPR-related symptoms are nonspecific and may be associated with other diseases such as allergy, smoking, infection, and muscle tension dysphonia in especially patients with no reflux. In addition, pharyngeal reflux episodes can differ from day to day, for example, no reflux during 1 day and several reflux episodes during another day in a single subject [21]. In fact, the potential differences in the results of MII-pH between days may be related to diet. The consumption of high protein foods improves the tonicity of the upper and lower esophageal sphincter, while carbonated beverage, caffeine, alcohol, fat, and tobacco are known to decrease the sphincter tonicity that promotes LPR and GERD [23, 24]. Though we emphasized all subjects to avoid meals which can generate reflux, other various factors other than meals need to be considered comprehensively. Thus, we checked retrograde fall in impedance between the two electrode pairs to distinguish reflux from artifacts from swallowing. In addition, air trapping which occurs when pharynx channel z1 or z2 is located too high above UES might influence the pharyngeal impedance. To reduce artifacts from air trapping, we located pharynx channel z1 and z2 at the exact location using nasopharyngolaryngoscope. Finally, the number of healthy subjects is relatively small compared to patients with suspected LPR. This might be probably because we strictly selected healthy subjects satisfying inclusion and exclusion criteria. In addition, 6 healthy subjects could not stand the maintenance of 24-h MII-pH monitoring and removed it themselves, and they were excluded from this study.

Unlike previous literatures, this report analyzed ROC curves, sensitivity, specificity, and accuracy comprehensively in patients with suspected LPR and healthy subjects to determine objective cut-off values of pharyngeal reflux episodes in LPR. In other words, this study is significant in terms of its approach to finding appropriate and objective diagnostic criteria for LPR. The application of 24-h MII-pH monitoring with an appropriate diagnostic cut-off value for patients complaining of LPR-related symptoms and showing LPR-related findings would increase the diagnostic accuracy of LPR.

In conclusion, a cut-off value of ≥ 1 in pharyngeal reflux episodes on 24-h MII-pH monitoring in patients with suspected LPR might be an appropriate diagnostic tool for LPR. Further studies of other parameters of MII-pH in larger subjects might be helpful for establishing more accurate diagnostic criteria of LPR.

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Author contributions YGE: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; SIK, SJJ, and YGE: study concept and design; SIK, OEK, JMP, JGD, and YCL: acquisition of data; SIK, SJJ, SIP, BHK, and SGK: analysis and interpretation of data; SIK, SJJ: drafting of the manuscript; SIP, BHK, YCL, and YGE: critical revision of the manuscript for important intellectual content; SIK, SJJ, BHK, and SGK: statistical analysis; BHK, YGE: study supervision.

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Availability of data and materials The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The authors obtained Kyung Hee University Medical Center Institutional Review Board (IRB) approval before the start of the study (IRB No. 2018–06-046). And, all subjects provided written informed consent before being included in this study.

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