Characteristics of 24-h multichannel intraluminal impedance-pH monitoring in patients with laryngopharyngeal reflux refractory to proton pump inhibitor therapy: A prospective cohort study

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Abstract

Objectives: This study evaluated the characteristics of reflux in patients with laryngopharyngeal reflux (LPR) refractory to proton pump inhibitor (PPI) therapy using the 24-h multichannel intraluminal impedance (MII)-pH monitoring. Design: Prospective cohort study. Setting: A tertiary care otolaryngology clinic. Participants: Patients with suspected LPR underwent 24-hour MII-pH monitoring and were prescribed high-dose PPI twice daily. One-hundred and eight patients followed up for at least 2 months were enrolled. Main outcome measures: Patients with suspected LPR showing more than one proximal reflux episode were considered to have LPR. Patients with LPR showing [?]50% decrease in the follow-up reflux symptom index (RSI) score compared to the pre-treatment RSI score during treatment periods were defined as responders; others were defined as non-responders. Various parameters in the 24-h MII-pH monitoring between non-responders and responders with LPR were compared using Student's t-test. Results: Of 108 patients with suspected LPR, 80 were diagnosed with LPR. Patients with LPR were categorized as non-responders (n = 19) and responders (n = 61). Proximal all reflux time and proximal longest reflux time in MII parameters were significantly higher in responders than in non-responders (p = 0.0040 and 0.0216, respectively). The proximal all reflux time >0.000517% was a better cut-off value to predict responders with LPR compared to the proximal longest reflux time >0.61 min (sensitivity + specificity: 1.317 vs. 1.291). Conclusions: The proximal all reflux time can be helpful to predict the response to PPI therapy and establish a personalized therapeutic scheme in patients with LPR.

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Running title:24-h MII-pH monitoring in refractory LPR

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Design: Prospective cohort study.

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Main outcome measures: Patients with suspected LPR showing more than one proximal reflux episode were considered to have LPR. Patients with LPR showing [?]50% decrease in the follow-up reflux symptom index (RSI) score compared to the pre-treatment RSI score during treatment periods were defined as responders; others were defined as non-responders. Various parameters in the 24-h MII-pH monitoring between non-responders and responders with LPR were compared using Student'st -test.

Results: Of 108 patients with suspected LPR, 80 were diagnosed with LPR. Patients with LPR were categorized as non-responders (n = 19) and responders (n = 61). Proximal all reflux time and proximal longest reflux time in MII parameters were significantly higher in responders than in non-responders (p = 0.0040 and 0.0216, respectively). The proximal all reflux time >0.000517% was a better cut-off value to predict responders with LPR compared to the proximal longest reflux time >0.61 min (sensitivity + specificity: 1.317 vs. 1.291).

Conclusions: The proximal all reflux time can be helpful to predict the response to PPI therapy and establish a personalized therapeutic scheme in patients with LPR.

Keywords: laryngopharyngeal reflux, multichannel intraluminal impedance (MII)-pH, proton pump inhibitor, refractory, proximal all reflux time

Key points

- Some patients with LPR do not experience remission of LPR symptoms despite long-term aggressive PPI therapy.
- Proximal all reflux times and proximal longest reflux time in various MII parameters were significantly higher in responders than in non-responders with LPR.
- The application of 24-h MII-pH monitoring can help personalize the therapeutic scheme and reduce the management cost for patients with suspected LPR.

Introduction

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissue related to direct and indirect effects of gastroduodenal content reflux, inducing morphological changes in the upper aerodigestive tract.[1] LPR is evaluated based on laryngeal symptoms and findings. Empirical proton pump inhibitors (PPIs) along with lifestyle modifications are mainly used to treat patients with suspected LPR.[1,2] However, some patients with suspected LPR do not experience remission of LPR symptoms despite long-term high-dose PPI therapy. This is because of various causes, such as patient compliance, lifestyle, and overdiagnosis of LPR.[3]

The 24-h multichannel intraluminal impedance (MII)-pH monitoring is most reliable to precisely detect the characteristics of reflux (acid vs. nonacid; gas vs. liquid) and diagnose LPR. Recent studies found that patients with suspected LPR refractory to PPI therapy did not exhibit abnormal findings in MII-pH monitoring.[4,5] However, some patients with LPR with proximal all reflux episodes [?]1 in 24-h MII-pH monitoring are refractory to PPI therapy.[6] It is unclear which patients with LPR might benefit from the PPI therapy. To the best of our knowledge, the association between response to PPI therapy and parameters of 24-h MII-pH monitoring in patients with LPR has not been studied.

This study aimed to (i) evaluate reflux characteristics in patients with LPR refractory to PPI therapy using 24-h MII-pH monitoring and (ii) identify parameters and associated values to predict the response to PPI therapy in such patients.

Materials and methods

Ethical considerations

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.

Study design, setting, and participants

Patients who visited a tertiary care otolaryngology clinic with LPR symptoms were investigated prospectively. In this study, sticking or lump sensation in the throat, troublesome cough, frequent throat clearing, and hoarseness or voice problems, were defined as LPR symptoms. Patients were examined with laryngoscopy by an ENT specialist during routine laryngeal examination, and LPR-related findings, such as ventricular obliteration, subglottic edema, thick endolaryngeal mucous, and posterior commissure hypertrophy were noted. Laryngeal endoscopic findings were recorded using the reflux finding score (RFS) to assess clinical severity of each patient.[7]

Inclusion criteria were age between 19 and 75 years and safe tolerance to unsedated laryngoscopy. Patients with history of malignancy or radiotherapy in head and neck region, and current pregnancy were excluded in this study. Patients with LPR symptoms matching the aforementioned criteria underwent 24-h MII-pH monitoring. All patients were instructed to discontinue PPI intake for 2 weeks and antacid or H_2 blocker intake for 1 week before 24-h MII-pH monitoring. They were advised lifestyle changes and prescribed high-dose PPIs twice (30 min before meals) daily for at least 2 months. Patients lost to follow-up within 2 months were excluded from this study.

All patients completed the reflux symptom index (RSI) questionnaire before treatment and during the monthly visit during treatment. The RSI is a highly validated survey with nine questions to assess the level of severity of LPR and estimate the response to treatment. It estimates the level of symptoms and their severity through a 6-point Likert scale, which ranges from 0 to 5. A high score indicates more severe symptoms, whereas 0 indicates no symptom.[8]

Patients with suspected LPR were classified into those with LPR (proximal all reflux episodes [?]1) and those with no reflux (proximal all reflux episodes = 0). Patients with LPR were divided into non-responders and responders according to the improvement of subjective symptoms in the RSI questionnaire. Those showing a [?]50% decrease in the follow-up RSI score compared to the pre-treatment RSI score during treatment were defined as responders; others were defined as non-responders.

Twenty-four-hour MII-pH monitoring and test interpretation

Insertion and analysis of MII-pH probe was conducted as described in previous studies.[9,10] The dual-channel MII-pH catheter models (ZAI-BL-54, 55, 56, ComforTEC Z/PH single use probe with 2.3 mm diameter; Sandhill Scientific, Inc., WI, USA) were selected according to the esophageal length of each patient, and inserted by two ENT doctors. Recorded data were manually analyzed by one expert (EUN YG) using a software program (BioView Analysis, Sandhill Scientific, Inc., Highlands Ranch, CO, USA).

The DeMeester score was calculated in the pH1 and pH8 areas as described previously.[10] The acid exposure time (%), reflux episode, and longest reflux time (min) at pH1 and pH8 were recorded. The acid exposure time was the total time of acid reflux episodes divided by the monitoring time. Acid reflux episodes was defined as a drop in pH to less than 4 for at least 5 s. The longest reflux time was expressed in minutes.[11]

Proximal MII parameters were recorded in reference to the two impedance sensors closest to the hypopharynx, and distal MII parameters were recorded in reference to the two impedance sensors closest to the lower esophageal sphincter. Six parameters were evaluated for proximal and distal MII parameters: (i) all reflux time (%); (ii) longest reflux time (min); (iii) number of acid reflux episodes; (iv) number of weak acid reflux episodes; (v) number of weak alkali reflux episodes; and (vi) number of all reflux episodes.

All reflux time (%) was defined as the sum of the bolus clearance time of all individual reflux episodes divided by the monitoring time. Reflux episodes were checked for liquid, gas, and mixed liquid-gas, respectively:[9] (i) A liquid reflux episode defined as a retrograde 50% fall in impedance from the mean baseline impedance

between the two consecutive impedance sites. (ii) A gas reflux episode defined as a rapid increase (3 kΩ/s) in two consecutive impedance sites with one site showing an absolute value >7 kΩ without swallowing. (iii) A mixed liquid–gas reflux episode defined as gas reflux occurring immediately before or during a liquid reflux episode.[12] Proximal and distal reflux episodes (liquid + gas + mixed) were classified based on the pH as acidic (<4), weakly acidic (between 4 and 7), or weakly alkaline (>7).

Statistical analysis

Statistical analyses were performed using a R software package (*http://www.r-project.org*). The chi-square test was used to compare differences in categorical variables between each group. The RSI, RFS score, treatment periods, and various parameters in the 24-h MII-pH monitoring between non-responders and responders with LPR were compared using Student's t -test. Ap -value <0.05 was considered to be statistically significant. Significantly different parameters in the 24-h MII-pH monitoring between two groups were analyzed using the receiver operating characteristic (ROC) curve to determine the cut-off value to predict responders with LPR.

Results

We enrolled 186 patients with suspected LPR who underwent 24-h MII-pH monitoring. All subjects were prescribed high-dose PPIs twice. However, 78 patients with suspected LPR were lost to follow-up after 2 months. Finally, 108 patients were included. Selection and grouping of patients with suspected LPR are summarized in the flowchart in Figure 1.

There were 28 patients (12 men and 16 women, mean age: 51.43 ± 12.62) with no reflux and 80 patients (31 men and 49 women, mean age: 55.24 ± 12.78) with LPR. There were no significant differences in age, sex, medical history (diabetes mellitus, hypertension), social history (alcohol, smoking, coffee), and pre-treatment RSI or RFS between patients with no reflux and those with LPR. However, the responder rates after treatment during 2 months were significantly higher in patients with LPR than in those with no reflux (57.50% vs. 28.57%, $p = 0.0157$; Table 1).

Patients with LPR were divided into non-responders (n = 19; 9 men and 10 women; mean age, 56.38 years) and responders (n = 61; 22 men and 39 women; mean age, 54.88 years). There were no significant differences in age, sex, medical history, social history, pre-treatment RSI or RFS, and medication periods between two groups (Table 2). Responders showed higher proximal MII parameters compared to non-responders (Table 3). All reflux time and longest reflux time in various proximal MII parameters were significantly higher in responders than in non-responders (p= 0.0040 and 0.0216, respectively; Figure 2A, B). However, there was no significant difference in the proximal all reflux episodes between two groups (p = 0.4781; Figure 2C). Also, there were no significant differences in distal MII parameters between two groups (Table 3).

The ROC curves used to determine the appropriated cut-off value of proximal all reflux time and proximal longest reflux time for predicting responders with LPR are depicted in Figure 3. The area under the ROC curves (AUCs) were 0.619 (95% confidence interval [CI], 0.488–749) and 0.624 (95% CI, 0.488–760) for proximal all reflux time and proximal longest reflux time, respectively (Figure 3). The cut-off values to predict responders with LPR were >0.000517% (sensitivity 47.5%, specificity 84.2%) for proximal all reflux time and >0.61 min (sensitivity 34.4%, specificity 94.7%) for proximal longest reflux time. The sensitivity plus specificity was higher for the cut-off value of proximal all reflux time than for that of proximal longest reflux time (1.317 vs. 1.291).

Discussion

Synopsis of key/new findings

Gastroesophageal reflux disease (GERD) and LPR are caused by the reflux of gastric contents and mainly treated with PPI therapy despite some differences in the clinical presentation and treatment modalities.[13] Most otolaryngologists prefer empirical PPI therapy during 1˜3 months,[14,15]and patients with LPR are expected to respond to acid suppression therapy of sufficient dose and duration. However, PPIs would not be

effective when nonacid components of refluxate lead to LPR.[16] Alternative treatments, such as alginate and magaldrate, are recommended but are not as commonly used as PPI. Therefore, in this study, we analyzed reflux characteristics in patients with suspected LPR treated with high-dose PPIs twice for at least 2 months prospectively.

MII-pH monitoring is a more objective diagnostic tool compared to symptomatic or laryngeal tools for diagnosing LPR.[17]However, many otolaryngologists do not frequently use MII-pH because of patient inconvenience and lack of tolerance, unclear indications, and a perceived lack of benefit for LPR management.[15]Empirical PPI treatment without an objective diagnosis using 24-h MII-pH monitoring in patients with suspected LPR can lead to prolonged treatment, high cost, and refractory progression despite long-term treatment. The responder rates after treatment during 2 months and total medication periods were significantly higher in patients with LPR than in those with no reflux according to the all proximal reflux episodes in the 24-h MII-pH monitoring. The use of 24-h MII-pH monitoring in patients with suspected LPR could be an important tool, probably because of its cost effectiveness and provision of symptomatic relief compared to empirical PPI therapy.

In addition, MII-pH monitoring includes parameters to systematically identify reflux in patients with LPR. All reflux time, longest reflux time, and reflux type at the hypopharynx and lower esophageal sphincter can provide detailed information about the reflux, but there is no standard for interpreting these parameters. Thus, we aimed to identify parameters showing differences between patients with LPR responding well and those refractory to PPI therapy. In this study, patients with LPR responding well to PPI therapy showed higher values in proximal MII parameters compared to those with LPR refractory to PPI therapy although there were no significant differences in proximal reflux episodes between two groups.

Additionally, we hypothesized that the ROC curve might help find appropriate cut-off values of proximal all reflux time and proximal longest reflux time to predict responders with LPR. We compared sensitivity and specificity according to each cut-off value in the two ROC curves. The sensitivity plus specificity was higher for the cut-off value of proximal all reflux time than for that of proximal longest reflux time (1.317 vs. 1.291). Thus, the cut-off value (>0.000517%) of proximal all reflux time was an appropriate value to predict responders with LPR despite the low sensitivity (47.5%) in this study. We know that 0.000517% of 24 h is equivalent to 44.67 s. In other words, patients with LPR showing proximal all reflux time of more than 45 s can be expected to respond well to PPI therapy.

Comparisons with other studies

In a previous study, most parameters of 24-h MII-pH monitoring did not reflect subjective symptoms in the RSI questionnaire in patients with LPR.[10] This seems to be due to the non-specificity of LPR-related symptoms, which may be associated with allergy, smoking, environment, toxic inhalant, infection, or voice abuse.[18] However, RSI is a validated patient-reported outcome measure and can be used to measure responsiveness to treatment during follow-up in patients with LPR.[8,19] Therefore, we investigated RSI continuously during treatment periods to classify patients with LPR into non-responders and responders.

In this study, proximal all reflux time and proximal longest reflux time were significantly higher in responders than in non-responders. Considering that there were no significant differences in the proximal reflux episode according to the reflux type between two groups, the duration of reflux into the pharynx seems to be more important for response to PPI therapy in patients with LPR. Moreover, there were no significant differences in distal MII parameters between two groups. Although the relationship between LPR and GERD is controversial, studies have considered LPR and GERD as different diseases.[13,20] Our study indirectly showed that the degree and type of gastroesophageal reflux do not significantly influence the response to PPI therapy in patients with LPR.

Strengths of the study

Unlike previous studies, this study analyzed various parameters of 24-h MII-pH monitoring in patients with LPR responding well and refractory to PPI therapy prospectively. We focused on parameters, such as

proximal all reflux time and proximal longest reflux time, which are apt to be overlooked in 24-h MII-pH monitoring when diagnosing LPR. We also compared the responder rates and treatment periods in patients with no reflux and those with LPR to assess the usefulness of empirical PPI therapy and the need for 24-h MII-pH monitoring in patients with suspected LPR.

Clinical applicability of the study

The application of 24-hour MII-pH monitoring in patients with LPR could help improve the therapeutic response. Especially, the proximal all reflux time ([?]45s) might play an important role to predict patients with LPR well responding to PPI therapy. Further studies on proximal parameters according to the reflux type in larger cohorts may help establish the cut-off value showing increased sensitivity and specificity to predict patients with LPR well responding to PPI therapy.

Conclusion

In conclusion, the proximal all reflux time in various 24-h MII-pH monitoring parameters can be helpful to predict the response to PPI therapy in patients with LPR. These findings will help establish a personalized therapeutic scheme and reduce the management cost for patients with suspected LPR.

Data availability statement

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

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Table legends

Table 1. Demographics of patients with suspected laryngopharyngeal reflux

Table 2. Demographics of patients with laryngopharyngeal reflux according to the response to proton pump inhibitor therapy

Table 3. Parameters of 24-h multichannel intraluminal impedance-pH monitoring in patients with laryngopharyngeal reflux according to the response to proton pump inhibitor therapy

Figure legends

Figure 1. Flowchart of this study

LPR, laryngopharyngeal reflux; MII, multichannel intraluminal impedance; PPI, proton pump inhibitor; RSI, reflux symptom index

Figure 2. Box plot showing differences in several proximal parameters of the 24-h multichannel intraluminal impedance (MII)-pH monitoring between non-responders and responders with laryngopharyngeal reflux (LPR). Responders showed a significantly higher proximal all reflux time and proximal longest reflux time compared to non-responders ($p = 0.0040$ and 0.0216, respectively; A, B). However, there were no significant differences in the proximal all reflux episodes between the two groups ($p = 0.4781$; C).

Figure 3. Receiver operating characteristic (ROC) curve analysis for determining the appropriate cut-off value of proximal all reflux time and proximal longest reflux time for predicting responders with laryngopharyngeal reflux (LPR). For proximal all reflux time, >0.000517% was the best cut-off value to predict

responders with LPR (A). For proximal longest reflux time, >0.61 min was the best cut-off value to predict responders with LPR (B).

AUC, area under the ROC curve; CI, confidence interval; Sens., sensitivity; Spec., specificity

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`Table.1-3.pdf` available at https://authorea.com/users/378499/articles/494980-characteristics-of-24-h-multichannel-intraluminal-impedance-ph-monitoring-in-patients-with-laryngopharyngeal-reflux-refractory-to-proton-pump-inhibitor-therapy-a-prospective-cohort-study