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Original Article

Validation of Pharyngeal Acid Reflux Episodes Using Hypopharyngeal Multichannel Intraluminal Impedance-pH

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Background/Aims
Hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH) technology incorporating 2 trans-upper esophageal sphincter impedance channels has been developed to detect pharyngeal reflux. We used the HMII-pH technique to validate the candidate pharyngeal acid reflux (PAR) episodes based on the dual-pH tracings and determined the interobserver reproducibility.

Methods
We conducted a cross-sectional study in tertiary centers in Taiwan. Ninety patients with suspected laryngopharyngeal reflux and 28 healthy volunteers underwent HMII-pH test when off acid suppressants. Candidate PAR episodes were characterized by pharyngeal pH drops of at least 2 units and reaching a nadir pH of 5 within 30 seconds during esophageal acidification. Two experts manually independently identified candidate PAR episodes based on the dual-pH tracings. By reviewing the HMII-pH tracings, HMII-pH-proven PAR episodes were subsequently confirmed. The consensus reviews of HMII-pH-proven PAR episodes were considered to be the reference standard diagnosis. The interobserver reproducibility was assessed.

Results
A total of 105 candidate PAR episodes were identified. Among them 84 (80.0%; 95% CI, 71.0-87.0%) were HMII-pH-proven PAR episodes (82 in 16 patients and 2 in 1 healthy subject). Patients tended to have more HMII-pH-proven PAR episodes than healthy controls (median and percentile values [25th, 75th, and 95th percentiles]: 0 [0, 0, 3] vs 0 [0, 0, 0], $P = 0.067$). The concordance rate in diagnosing HMII-pH-proven PAR episodes between 2 independent observers was 92.2%.

Conclusion
Our preliminary data showed that 80.0% (71.0-87.0%) of the proposed candidate PAR episodes were HMII-pH-proven PAR episodes, among which the interobserver reproducibility was good.
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Key Words
Acids; Esophagus; Gastroesophageal reflux

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Introduction

Pharyngeal acid reflux (PAR), defined as acidic refluxate arising from the stomach into the laryngopharynx, has been proposed as the gold standard for diagnosing laryngopharyngeal reflux (LPR) according to the American Academy of Otolaryngology-ENT guidelines.[1] However, objective diagnosis remains uncertain as current PAR detection technologies lack a standardized methodology and interpretation, including dual-pH monitoring, oropharyngeal pH monitoring, salivary pepsin test, and pH-impedance monitoring.[2] More importantly, no outcome studies have been conducted to confirm the relevance of these devices.

Among various diagnostic modalities, multichannel intraluminal impedance-pH monitoring is the most reliable technique for the detection of reflux episodes and the associated proximal extent, acidity, and physical properties (liquid or gas) of refluxate.[2] The hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH) technique incorporating 2 trans-upper esophageal sphincter (UES) impedance sensors is specifically designated to detect pharyngeal reflux episodes. The device may theoretically differentiate refluxes (retrograde impedance change) from swallows (antegrade impedance change) so that refluxate may be tracked along the entire esophagus and into the hypopharynx.[3] However, the validity of this technique is questionable largely because of poor interobserver reproducibility.[4]

Using 3-pH-sensor catheters, we previously proposed candidate PAR episodes derived from Williams et al,[5] ie, a pharyngeal pH drop of greater than 2 units and reaching a nadir pH of below 5 within 30 seconds during esophageal acidification and found good interobserver reproducibility.[6] Although our proposed diagnostic parameter has not been validated, we recently found that patients with a positive composite pH parameter, defined as ≥ 2 candidate PAR episodes and/or excessive esophageal acidic exposure time at baseline were 4.9-fold (1.8-13.3) and 4.0-fold (1.7-9.3) more likely to respond to proton pump inhibitors therapy at 12 weeks in those with isolated LPR symptoms as well as in those with concomitant typical reflux symptoms, respectively, than in those with a negative pH, suggesting a potential diagnostic role in managing LPR.[7] Recently, Rogers et al[8] found that acidic episodes with high proximal extent on esophageal impedance-pH studies appeared to have a high concordance for identification by expert reviewers. Given the acidic nature and high proximal extent of PAR episodes, we hypothesized that HMII-pH technique could be used to validate the candidate PAR episodes with good interobserver reproducibility.

In this study, we validated the proposed candidate PAR episodes using HMII-pH technique and assessed the interobserver reproducibility of the technique.

Materials and Methods

This prospective multicenter study was conducted at Taichung Veterans General Hospital, China Medical University Hospital, and Chung Shan Medical University Hospital, Taiwan. Patients underwent examinations in the Gastrointestinal Physiology Laboratory, Otolaryngology Laboratory, and Pulmonary Laboratory. The Institutional Review Board of Taichung Veterans General Hospital approved this protocol (#CF16150B). All of the participants signed an informed consent form prior to the study procedures.

Subjects

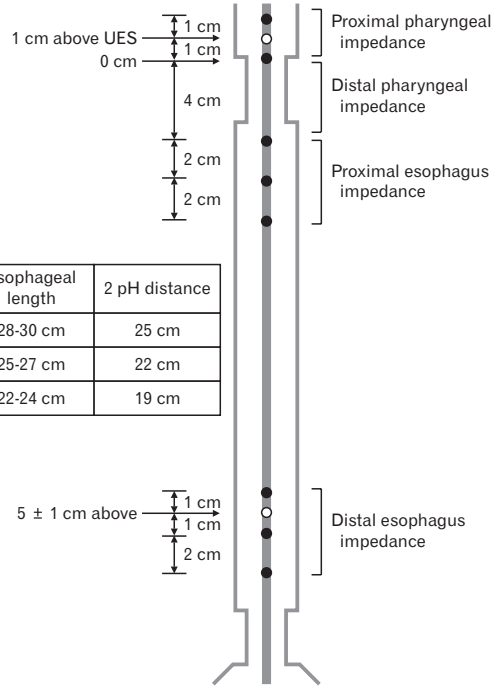
Patients with suspected LPR symptoms referred from otorhinolaryngologic clinics between August 2016 and December 2019 were recruited and evaluated for eligibility. The inclusion criteria were major laryngeal symptoms with at least moderate severity for more than 3 months, laryngoscopic signs suggestive of reflux, and age 20 years or older. We excluded subjects with any common non-reflux etiologies of chronic laryngitis, as stated previously.[7] Healthy volunteers were recruited by distributing flyers. Subjects with respiratory or upper gastrointestinal symptoms or disorders such as esophagitis, Barrett's esophagus, or tumors were excluded.

Study Design

All participants underwent esophagogastroduodenoscopy (GIFXQ-240; Olympus, Tokyo, Japan) prior to the esophageal motility tests. After overnight fasting, each participant underwent a high-resolution manometry test (Solar GI HRM, MMS, Enschede, The Netherlands) to locate the positions of the upper mar-

gins of the upper and lower esophageal sphincters (UES and LES). Subsequently, a HMII-pH catheter with a distance of 19 cm, 22, cm, or 25 cm between 2 pH sensors was chosen based on the esophageal length for detection of both esophageal and hypopharyngeal refluxes (catheter models CZAIBL-54, -55, and -56; Sandhill Scientific, Inc, Highlands Ranch, CO, USA). To maximize the hypopharyngeal recording, we placed the pH sensor at 1 cm above the manometrically determined UES,[9] as the hypopharyngeal sensor was more important in this patient group. Thus, the esophageal pH sensor was positioned at 5 ± 1 cm above the upper margin of the LES. There were 6 impedance electrode pairs, with 2 located at the hypopharynx (1 cm above UES and trans-UES), proximal esophagus (2 cm and 4 cm below UES), and distal esophagus (3 ± 1 cm and 5 ± 1 cm above LES), respectively (Fig. 1).

The catheters were calibrated in pH 4.0 and pH 7.0 buffer solutions immediately before and after the experiments. Data sampling frequency was 50 Hz for both pH and impedance. During the 24-hour recording period, participants were instructed to maintain regular activities except bathing, to keep their usual dietary habits except avoidance of acidic beverages, to keep a detailed diary including meal times, body position (upright or recumbent), and symptoms, and not to take any anti-reflux medications.



	Esophageal length	2 pH distance
ZAI-BL-54	28-30 cm	25 cm
ZAI-BL-55	25-27 cm	22 cm
ZAI-BL-56	22-24 cm	19 cm

Figure 1. Configuration of the hypopharyngeal multichannel intraluminal impedance-pH catheter for detection of pharyngeal acid reflux. The catheter was selected based on the participants' esophageal length. The catheter incorporates 2 trans-upper esophageal sphincter (UES) impedance channels to differentiate refluxes from swallows, 2 proximal esophageal ones, and 2 distal esophageal ones. The 2 pH probes were located at 1 cm above the UES and 5 cm (± 1 cm) above the lower esophageal sphincter (LES).

Data Analysis

Tracings were analyzed with the assistance of the Bioview Analysis software (version 5.7.1.0; Sandhill Scientific, Inc). Meal times were not analyzed. Two trained experts (H.C.L. and Y.Y.C.) independently screened for possible PAR episodes by selecting esophagopharyngeal pH drops manually in 3 steps: (1) We visually inspected the dual-pH tracings with a time window of 1 hour computer screen. All of the abrupt pharyngeal pH drops of at least 2 units to a nadir pH below 5 within 30 seconds during esophageal acidification (pH < 4) were selected, while isolated pharyngeal pH drops were excluded based on the assumption that genuine PAR is only possible when preceded by esophageal acidification; (2) With adequate zooming in of dual-pH tracings, artifacts such as slow downward pH drift, ie, > 30 seconds to nadir pH, abrupt pH return to baseline, and out of range (pH = 0 or > 8) were excluded.[10] Additionally, synchronous and antegrade esophagopharyngeal pH drops were also excluded as these were likely due to equipment-related and swallow-induced artefacts, respectively (Fig. 2A-C); and (3) The remaining retrograde esophagopharyngeal pH drops were considered to be candidate PAR episodes. All of the selected episodes of dual-pH drops including possible artifacts and candidate PAR episodes were subsequently validated against reference standard diagnosis of PAR episodes based on HMII-pH tracings by the consensus review of 3 trained experts (H.C.L., Y.Y.C., and C.S.C.).

A HMII-pH-proven PAR episode was defined as a retrograde 50% drop in baseline impedance starting from the more distal esophageal channel (at the level of 3 ± 1 cm above upper margin of the LES) to the more proximal pharyngeal channel (at the level of 1 cm above upper margin of the UES) occurring during the period of retrograde esophagopharyngeal pH drops. Furthermore, a PAR episode was only considered when the nadir in both pharyngeal impedance sensors was less than 1200 ohms,[11] preceded by a retrograde impedance drop in full column reflux of esophagus, and if no swallow occurred during the pharyngeal impedance drop (Fig. 2D-F). The reason for choosing the strict criterion of 1200 ohms for liquid pharyngeal reflux was because the impedance value is often > 10 000 ohms when air is trapped between the catheter and the pharyngeal mucosa, and may drop to 2000-5000 ohms when there

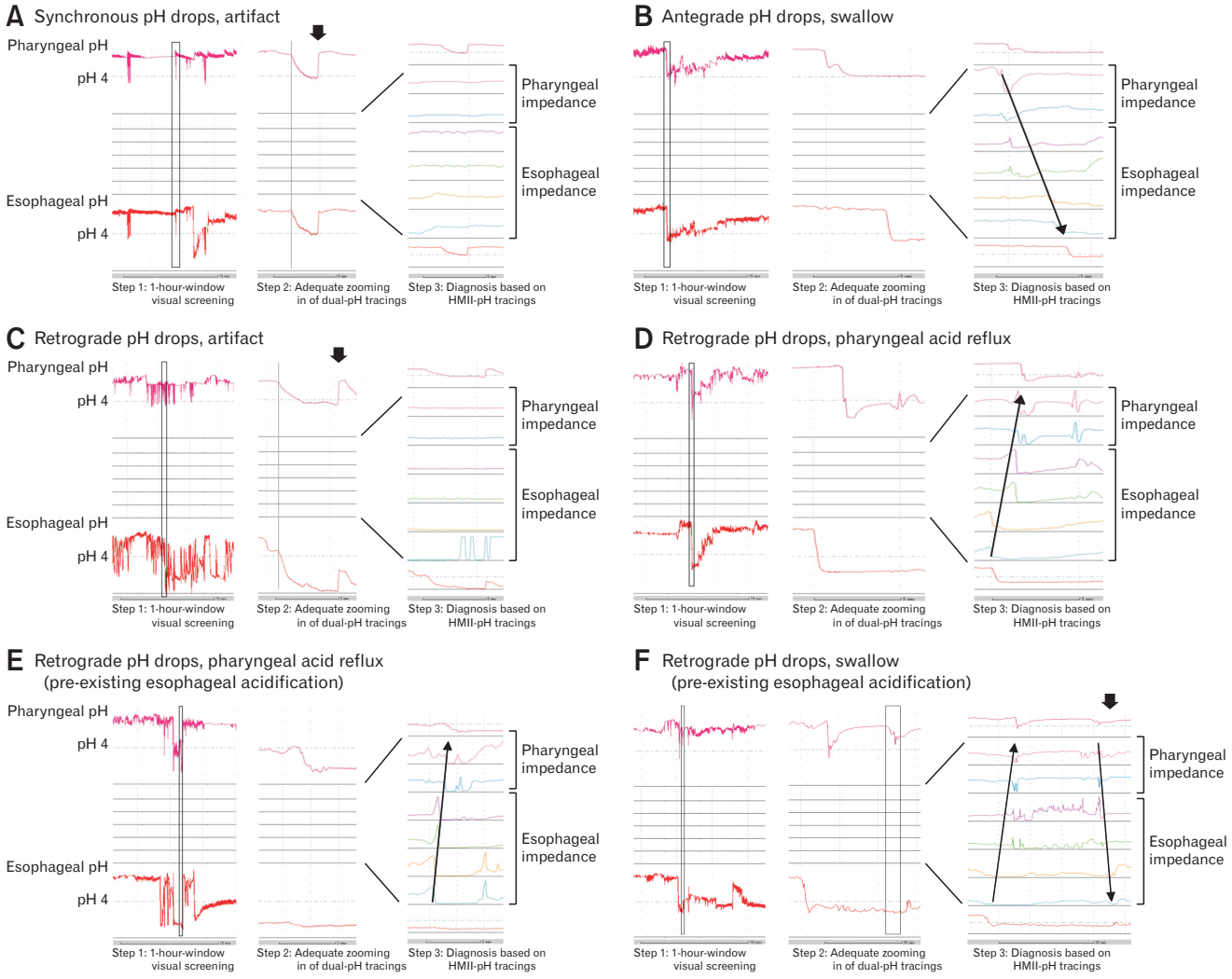


Figure 2. Examples of representative artifacts, swallows, and pharyngeal acid reflux (PAR) episodes based on visual analyses of 1-hour window screening (step 1) and adequate zooming in (step 2) of the dual pH tracings. Final diagnosis was made based on the magnified hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH) tracings (step 3). (A) Synchronous pH drops were characterized as onset of pH drops occurring simultaneously in both pharyngeal and esophageal channels during adequate zooming in (solid vertical line in step 2), which were most likely due to equipment errors. Moreover, abrupt pH return to baseline (arrowhead) also simultaneously occurred in both channels. (B) Antegrade pH drops were characterized as pharyngeal pH drops followed by esophageal pH drops, in which an acidic liquid swallowing episode outside of meals was diagnosed by HMII-pH tracings (step 3). (C) Retrograde pH drops characterized as pharyngeal pH drops (vertical line), preceded by esophageal pH drops. However, simultaneous abrupt pH return to baseline (arrowhead) in both channels (step 2) suggests artifacts, which were subsequently proved by HMII-pH tracings in step 3. (D) Retrograde pH drops typically occur in a PAR episode when an esophageal pH drop is followed by a pharyngeal pH drop. (E) Retrograde pH drops could also exist in a PAR episode during a prolonged or pre-existing esophageal acidification. (F) Retrograde pH drops due to acidic liquid swallows (arrowhead) may occur immediately after a PAR episode, suggesting a possibility of re-swallowing hypopharyngeal acidic refluxate.

is contact between the two.

We only analyzed pure liquid and mixed liquid-gas PAR episodes. The latter was defined as a gas reflux occurring immediately before or during a liquid reflux. Gas reflux was defined as a rapid (3000 ohms/sec) increase in at least 2 esophageal impedance channels simultaneously of > 5000 ohms in the absence of swallowing. We did not analyze pure gas PAR episodes because it is difficult to differentiate air trapped from gas reflux when the catheter is not in contact with the pharyngeal mucosa. A liquid swallow was defined as an antegrade impedance drop starting from the more proximal

pharyngeal channel to the proximal esophageal channels or beyond (Fig. 2B).

Statistical Methods

Numerical data such as ages and body mass index are expressed as means (±SD), while acid reflux parameters are expressed as median and percentile values (25th, 75th, and 95th). We used independent *t* test to analyze age and body mass index, and the Mann-Whitney *U* test to analyze acid reflux parameters. Categorical data such as gender, presence of erosive esophagitis, presence of pathological reflux, and hiatus hernia were analyzed using univariate logistic regression analysis. Using the consensus reviews as the reference standard diagnoses, percentage of PAR episodes correctly diagnosed by both observers and percentage of missed and misdiagnosed episodes by each observer were calculated. Interobserver reproducibility of candidate PAR episodes, full column reflux, pharyngeal reflux, and HMII-pH-proven PAR episodes was determined by the concordance, calculated as the number of episodes detected independently by both observers divided by the number of episodes detected by at least one observer.

Table 1. Demographic Data of the Study Population

Demography and clinical characteristics	Patients (n = 90)	Healthy control (n = 28)	*P*-value
Demography			
Age (yr)	55.3 ± 10.2	43.3 ± 13.3	< 0.001
Male gender	70/90 (77.7)	11/28 (39.2)	< 0.001
BMI (kg/m^2)	23.7 ± 3.3	22.7 ± 3.1	0.152
ENT first visit	73/90 (81.1)	-	-
Clinical presentations			
Major laryngeal symptom			
Globus sensation	22/90 (24.4)	-	-
Throat pain	19/90 (21.1)	-	-
Hoarseness	31/90 (34.4)	-	-
Cough	15/90 (16.6)	-	-
Throat clearing	3/90 (3.3)	-	-
Typical GERD symptoms	34/90 (37.7)	-	-
Symptom duration, months	12 (7, 36)	-	-
Previous acid suppressive therapy use	61/90 (67.7)	-	-
Diabetes mellitus	5/90 (5.6)	0/28 (0.0)	0.337
Hypertension	17/90 (18.8)	1/28 (3.6)	0.069
Post nasal drip	37/90 (41.1)	0/28 (0.0)	< 0.001
Endoscopic findings			
Reflux esophagitis	10/90 (11.1)	0/28 (0.0)	0.115
Hiatus hernia	4/90 (4.4)	0/28 (0.0)	0.571
Peptic ulcer	7/90 (7.8)	5/28 (17.8)	0.237
Helicobacter pylori	21/90 (23.3)	9/27 (33.3)	0.698
24-hour pH test finding			
Distal esophageal pH time (%)			
Total	0.8 (0.2-2.1, 7.8)	0.3 (0.1-1.2, 2.9)	0.094
Upright	1.2 (0.3-3.1, 10.5)	0.5 (0.2-1.8, 3.2)	0.073
Supine	0.0 (0.0-0.1, 3.9)	0.0 (0.0-0.0, 3.5)	0.366
Pathological acid exposure time in the distal esophagus[a]	17/90 (18.8)	3/28 (10.7)	0.398

[a]Pathological acid exposure time in the distal esophagus was defined as ≥ 4.2% of 24-hour, or ≥ 6.3% of upright position, or ≥ 1.2% of supine position, with pH < 4 at 5-cm above the upper margin of the lower esophageal sphincter.
BMI, body mass index; ENT, Ear-Nose-Throat specialists; GERD, gastroesophageal reflux disease.
Pearson chi-square tests were used for dichotomous variables, whereas Mann-Whitney *U* tests were used for continuous variables, *t* tests were used when age and BMI were expressed as continuous variables (normal distribution).
Data are presented as mean ± SD, n/n (%), or median (interquartile range).

Results

Subjects

A total of 117 patients and 57 healthy controls were recruited to evaluate their eligibility for inclusion in the study; 90 patients and 28 healthy subjects completed the tests (Supplementary Fig. 1). The mean age was older (55.3 ± 10.2 vs 43.3 ± 13.3) in the patient group than in the healthy controls. Males were predominant in patients but not in healthy controls (77.7% vs 39.2%). Body mass index was comparable between the 2 groups. The vast majority of patients visited otolaryngologists first for their primary laryngeal symptoms, while only a minority had esophagitis (11.1%), hiatal hernia (4.4%), and concomitant typical reflux symptoms (37.7%) (Table 1). Pathological acid exposure time in the distal esophagus tended to be more common in patients than in healthy controls but without statistical significance (18.8% vs 10.7%, $P = 0.398$), while the median number of acidic reflux episodes in the distal esophagus was significantly higher in patients than that in healthy controls ($P = 0.004$) (Supplementary Table).

Pharyngeal Acid Reflux Episodes

A total of 105 candidate PAR episodes were identified. Among them, 84 (80.0%, 95 CI, 71.0-87.0%) were diagnosed as PAR episodes by HMII-pH tracings, ie, HMII-pH-proven PAR episodes. Examples of HMII-pH-proven PAR episodes, swallows, and artifacts in each step are depicted in Figure 2. None of the synchronous or antegrade esophagopharyngeal pH drops suspected by dual-pH tracings were HMII-pH-proven PAR episodes. The majority (81 of 84, 97.4%) of HMII-pH-proven PAR episodes occurred in an upright position; only 3 were recorded in a supine position. Only 1 episode was temporally associated with the symptom of regurgitation reported by a patient. In addition, 36 of 84 (43.0%) occurred in the postprandial period (within 1 hour after meal). There were 53 liquid and 31 mixed liquid-gas HMII-pH-proven PAR episodes. The durations of the HMII-pH-proven PAR episodes ranged from 0.1 seconds to 19.6 seconds, with a median of 1.9 seconds and 25th ,75th ,and 95th percentiles of 1.1, 4.2, and 8.9 seconds, respectively (Supplementary Fig. 2).

There were 82 HMII-pH-proven PAR episodes occurring in 16 patients and only 2 episodes occurring in 1 healthy subject. The number of HMII-pH-proven PAR episodes was marginally higher in patients than that in healthy controls (median [25th, 75th, 95th percentiles]: 0 [0, 0, 3] vs 0 [0, 0, 0], $P = 0.067$, Supplementary Fig. 3). Patients with pathological esophageal acid exposure time had a higher rate of HMII-pH-proven PAR episodes than those without (41.0% vs 12.0%, $P = 0.010$). The major laryngeal symptoms among patients with evidence of HMII-pH-proven PAR episodes were cough (n = 6), followed by hoarseness (n = 5), globus (n = 3), sore throat (n = 1), and throat clearing (n = 1). The only healthy subject who had 2 HMII-pH-proven PAR episodes had normal acid exposure time in the distal esophagus.

Interobserver Reproducibility

Among 84 HMII-pH-proven PAR episodes determined by consensus reviews, 83 (98.8%) were diagnosed by both observers. Number of missed or misdiagnosed episodes were rare. (Fig. 3) Table 2 shows the high concordance rates for diagnosing candidate PAR episodes, full column reflux, pharyngeal reflux, and HMII-

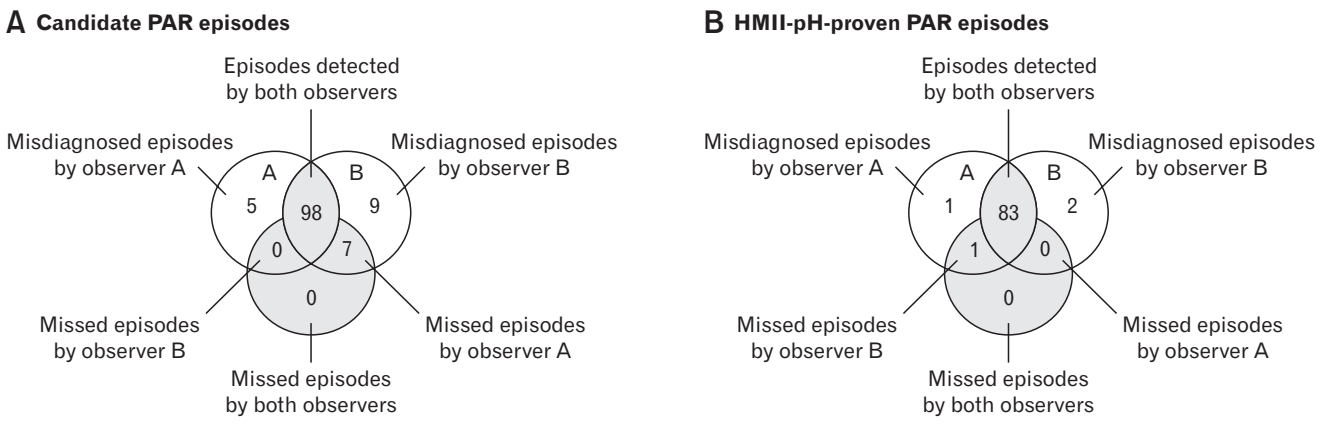


Figure 3. Number of candidate pharyngeal acid reflux (PAR) episodes (A) and hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH)-proven PAR episodes (B) detected by 2 independent observers. Gray zone represents episodes by 3 experts' consensus reviews.

Table 2. Concordance Rates of Diagnosing Candidate Pharyngeal Acid Reflux and Hypopharyngeal Multichannel Intraluminal Impedance-pH-proven Pharyngeal Acid Reflux Episodes Between 2 Independent Observers

HMII-pH measurements	Concordance rates between 2 observers (%)
Candidate PAR episodes	88.2% (105/119)
Impedance	
Full column reflux	98.9% (94/95)
Pharyngeal reflux	92.3% (84/91)
HMII-pH-proven PAR episodes	95.4% (83/87)

PAR, pharyngeal acid reflux; HMII-pH, hypopharyngeal multichannel intraluminal impedance-pH.

Table 3. Reasons and Number of Candidate Pharyngeal Acid Reflux Episodes That Do Not Fulfill the Definition of Hypopharyngeal Multichannel Intraluminal Impedance-pH-proven Pharyngeal Acid Reflux Episodes by Experts' Consensus Reviews

Post-PAR re-swallows of acidic refluxate	8
Post-PAR episode pH artifact	1
Post-esophageal-reflux reflexive swallows with acidic liquid	2
Equivocal candidate PAR episode	1
Full column reflux along with air trapped in pharyngeal impedance channels	6
Full column reflux along with pharyngeal nadir impedance greater than 1200 Ω	3

PAR, pharyngeal acid reflux.

pH-proven PAR episodes between 2 independent observers. Table 3 shows the reasons of false positivity of the candidate PAR episodes.

Discussion

In this study, we hypothesized that the HMII-pH technique would be capable of diagnosing PAR episodes with good interobserver reproducibility. Using this technique, we also validated our previously proposed criteria for candidate PAR episodes derived from Williams et al,[5,6] ie, a rapid pharyngeal pH decrease of at least 2 units, reaching a nadir pH of less than 5 within 30 seconds during esophageal acidification. We found 80.0% (71.0-87.0%) of candidate PAR episodes were HMII-pH-proven PAR episodes and there was good interobserver reproducibility of the technique based on our proposed criteria. Conversely, none of the equipment-related (synchronous esophagopharyngeal pH drops) or swallow-induced (antegrade esophagopharyngeal pH drops) episodes with magnification were HMII-pH-proven PAR episodes.

Our findings of rare PAR episodes in healthy controls are in line with those reported by Hoppo et al[3] who found a median and a 95th percentile of both 0 in 34 subjects, but were lower than that by Zerbib et al[4] who found a median of 0 and a 95th percentile of 3 in 46 subjects. This may be attributable to our strict PAR criteria which excluded weakly alkaline reflux and parts of weakly acid reflux episodes with a nadir pH between 5 and 7, while the other 2 studies analyzed pharyngeal reflux episodes regardless of nadir pH values. Another possible explanation is our strict definition of healthy controls. We excluded 16 asymptomatic reflux esophagitis patients during recruitment, while endoscopic screening was not done in Zerbib's study. The prevalence of asymptomatic reflux esophagitis was estimated to be as high as 5.7% in Western communities,[12] and was also not rare in Taiwan.[13,14] Lastly, despite only 2 HMII-pH-proven PAR episodes found in 1 healthy volunteer, the small sample size of our study may have resulted in lower precision.

There is a lack of uniform or accepted universal criteria for PAR episodes.[1,2] Factors contributing to the inconsistent results among studies include pharyngeal pH sensor locations, number of impedance sensors in the pharynx, definition of pharyngeal reflux (acid or nonacid, gaseous, or liquid), artifacts, and poor interobserver reproducibility.[15-17] Among these, swallow-induced artifacts seem to be common in pharyngeal recordings. Desjardin et al[18] found that 86.6% of simultaneous esophageal and pharyngeal pH drops were swallow-induced artifacts. However, with adequate zooming in, the vast majority of swallow-induced artifacts in our study could be identified as antegrade esophagopharyngeal pH decreases, while some were demonstrated to be retrograde esophagopharyngeal pH decreases occurring immediately after a PAR episode (Fig. 2F). The latter may be due to re-swallow of hypopharyngeal acidic refluxate[17] and may constitute the false positivity of candidate PAR episodes in our study (Table 3).

Although manual analysis of pharyngeal signals is notoriously difficult and time-consuming, high concordance between observers for both candidate PAR episodes and HMII-pH-proven PAR episodes in our study can be explained, in part, by the fact that only acidic reflux episodes in the retrograde esophagopharyngeal pH decreases were considered, and also by the characterization of PAR episodes such as high proximal extent and the upright positions.[8] Moreover, the high concordance of 95.4% (83/87) for interpreting retrograde pharyngeal impedance changes between observers in our study suggests the feasibility of HMII-pH tracing in differentiating refluxes from swallows. In future research artificial intelligence could be applied to facilitate the interpretation objectively based on the findings of the current study.

There were limitations in the present study. First, the candidate PAR episodes criteria proposed in this study did not consider pharyngeal refluxate with pH above 5 and esophageal refluxate with pH above 4, as well as pure gas refluxes, and thus pharyngeal reflux episodes may have been underestimated. However, the higher the pH value is, the less noxious is the effect of pepsin on the mucosa.[19] From the viewpoint of treatment outcome by acid suppressants, our proposed candidate PAR episodes combined with pathological acid exposure in the distal esophagus, could be used to predict response to proton pump inhibitors therapy at 12 weeks in our previous studies.[7,20] Secondly, the reproducibility of proximal esophageal reflux has been questioned.[21] Thus, future studies should evaluate the day-to-day variations of PAR episodes in healthy subjects as well as in patients with suspected LPR.

In conclusion, our preliminary data showed that candidate PAR episodes criteria defined as retrograde esophagopharyngeal pH decreases of $>$ 2 units, reaching a nadir pH of $<$ 5 within 30 seconds have an acceptably high positive predictive value in the diagnosis of HMII-pH-proven PAR episodes. In addition, interobserver reproducibility is high in the diagnosis of HMII-pH-proven PAR episodes based on our proposed candidate PAR criteria. Future large-scale studies to confirm our findings in patients with suspected LPR are warranted.

Supplementary Materials

Note: To access the supplementary table and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm22047.

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Conflicts of interest: None.

Author contributions: Han-Chung Lien and Chen-Chi Wang conceived and designed the experiments; Yen-Yang Chen, Chen-Chi Wang, Ying-Cheng Lin, Chun-Yi Chuang, Yung-An Tsou, Sheng-Shun Yang, Chi-Sen Chang, and Han-Chung Lien performed the experiments; Yen-Yang Chen, Han-Chung Lien, Chi-Sen Chang, and Ja-Chih Fu analyzed the data; and Yen-Yang Chen, Han-Chung Lien, and John Y Kao wrote the manuscript and approval of the final version.

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