Dual pH Probes Without Proximal Esophageal and Pharyngeal Impedance May Be Deficient in Diagnosing LPR

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Summary: Background. Laryngopharyngeal reflux (LPR) is commonly treated with empiric acid suppression. More evidence points to pepsin in the pathophysiology of LPR. Previous studies have evaluated esophageal impedance in patients who had previously failed high dose proton pump inhibitor (PPI) using older catheters without proximal esophageal (just under the upper esophageal sphincter) and pharyngeal impedance sensors. The aim of this study was to compare what traditional diagnostic tools, used for esophageal reflux, would detect and diagnose compared with what a combined hypopharyngeal-esophageal MII catheter with dual pH (HEMII-pH) can detect in the esophagus and pharynx in patients with suspected LPR.

Methods. Forty-two subjects with presumed LPR were referred for HEMII-pH testing. The number of distal and proximal esophageal impedance events, number of pharyngeal impedance events, symptom correlation, and event acidity were recorded. Previous normative values (>1 pharyngeal impedance events every 24 hours) were used to designate what was pathological LPR on HEMII-pH.

Results. Forty-two total subjects had pharyngeal impedance sensor data recorded. Twelve (28.6%) of the subjects were tested while taking high-dose PPI therapy. The mean number of proximal esophageal events was 23.3. The mean number of pharyngeal impedance events was 10. Thirty-four subjects (81%) tested positive for pharyngeal reflux. All patients who tested positive using traditional proximal impedance criteria also tested positive using pharyngeal criteria. Of patients who tested negative using traditional criteria, 72% were positive based on pharyngeal criteria.

Conclusions. HEMII-pH catheters should be considered in patients with LPR symptoms. Traditional criteria used for diagnosing esophageal reflux may not translate into LPR.

Level of Evidence: 2b.

Key Words: Reflux−Impedance testing−LPR−laryngopharyngeal reflux−GERD.

INTRODUCTION

Laryngopharyngeal reflux (LPR) symptoms are often treated empirically with acid suppression.[1] While proton pump inhibitor (PPI) therapy may neutralize the acidity of gastric reflux, it may not decrease the total number of reflux events taking place.[2] There is growing evidence that pepsin from the stomach is likely to play a role in causing LPR symptoms, and therefore acid suppression may not be sufficient by itself.[3] Growing concern over PPI side effects demands that the use of PPI medications decrease or at least be limited to those patients for whom they are truly indicated.[4] However, the opposite appears to be happening, as empiric PPI treatment for LPR seems to be routinely overprescribed by PCPs and specialists alike.[5,6]

Multichannel intraluminal impedance and pH testing is considered the current gold standard in reflux testing, and there are validated criteria for diagnosing esophageal reflux, including LPR.[7] These criteria, for example more than 31 impedance events in the "proximal" esophagus (15 cm above the lower esophageal sphincter [LES]) or acid events beyond the upper esophageal sphincter (UES), have been evaluated using subjects typically chosen through subjective patient-reported outcome measures such as the Reflux Symptom Index (RSI) and the equally subjective Reflux Finding Score (RFS).[7,8,9,10] The validity of diagnosing LPR using these criteria as well as using pharyngeal-only pH (Dx-pH Catheter; Restech, San Diego, CA) detection is controversial.[11,12,13] Clearly many subjects in prior studies have true LPR (reflux events above the UES) because acid was detected above the UES; and when objectively proven LPR was corrected with antireflux surgery, both the RSI and the RFS improved.[14] But one must question if all LPR events and potential LPR patients were captured in these studies, knowing now that nonacid reflux and pepsin play a significant role in the pathophysiology of LPR, as they would not have been detected with the technology used at the time. These studies were performed before the availability of the newest impedance technology that affords the demonstration of actual reflux events that begin in the lower esophagus and travel to the highest impedance electrodes above the UES. In other words, despite the ability of dual-pH probes to detect acid events in the pharynx and older impedance catheters to detect nonacid reflux up to 15 cm above the LES, nonacid events carrying pepsin at or above the UES were not specifically detected on any of these prior studies.

Establishing not just the existence of, but more importantly symptomatic pharyngeal reflux in patients with LPR

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symptoms is less straightforward. We know that pepsin clears from the pharynx after antireflux surgery and LPR symptoms improve; however, pH-only tests and impedance catheters that only go 15 cm above the LES will not capture all potentially deleterious events.[3] There is evidence that antireflux surgery is successful in patients selected using a hypopharyngeal-esophageal MII catheter with dual pH (HEMII-pH) to detect true LPR in patients with chronic cough.[15] However, the symptom association detected on HEMII-pH in LPR does not appear to be as useful or conclusive as it is in GERD patients.[15]

There are normative data to suggest that as few as two pharyngeal impedance events in 24 hours may be abnormal.[16] However, not all providers may have access to HEMII-pH catheters, and the value of established distal and proximal esophageal impedance criteria in predicting pharyngeal events is not known. The aim of this study was to compare what traditional diagnostic criteria used for esophageal reflux would detect and diagnose compared with what a HEMII-pH catheter can detect in the proximal esophagus and pharynx in patients with suspected LPR.

METHODS

Subject selection

IRB approval was obtained. We conducted a retrospective chart review of adult patients (age > 18 years) sent to our center for HEMII-pH testing for suspected LPR after failed high-dose PPI trial (40 mg daily, or equivalent, for 8 weeks) from April 2015 until October 2016. All patients were initially seen by an otolaryngologist with subspecialty training in laryngology (TC) and were suspected of having LPR based on history and correlation with laryngoscopic and/or stroboscopic exam. Patients may have had other laryngeal pathologies present, but LPR was still suspected to play a role in the presenting symptoms, warranting referral for HEMII-pH testing. Patients tested both on and off PPI were included, and appropriate normative data for esophageal impedance criteria were applied to each group as it has been shown that the number, proximal extent, and duration of reflux events do not change based on acid suppression.[2,17]

Medical records were reviewed, and demographic and clinical data were extracted, including age, sex, body mass index (BMI), smoking status, and history of typical GERD symptoms. Patients were also asked to complete the RSI and the Voice Handicap Index (VHI) 10 questionnaires prior to referral for HEMII-pH, and these scores were collected.

HEMII-pH testing

Exposure to reflux was objectively assessed by HEMII-pH. All patients underwent testing after an overnight fast. The HEMII-pH detection system consists of a portable electronic data logger and transnasal catheter (ComforTec Z/pH probes, ZAI-BL-26, 27, or 28; Sandhill Scientific Inc., Highlands Ranch, CO) equipped with two pH sensors and eight esophageal impedance electrodes with locations above the UES and within the esophageal body: 2 *pharyngeal* impedance pairs made up by the electrodes 3 and 1 cm above the UES and 1 cm above and 1 cm below the UES (0 cm is at the UES); 2 *proximal esophageal* impedance pairs made up by the electrodes at 1 and 3 cm below the UES and 3 and 5 cm below the UES; as well as 2 *distal* esophageal impedance electrode pairs made up by the electrodes at 9, 11, and 13 cm from the UES. For clarification, the term 'proximal' when referring to impedance reflux has had variable meaning in the literature but has traditionally meant as measured 15 cm above the lower esophageal sphincter (LES) which would approximate with the electrode 9 cm from the UES in the catheter configuration used in the current study. In our patients, *proximal esophageal* refers to the 2 electrode pairs closest to the UES (1 to 5 cm below, approximately 20 to 24 cm above the LES assuming a 25 cm esophagus) and within the esophagus while *pharyngeal* refers to the two UES electrode pairs (one within and one above).

The catheter was placed into the esophagus based on distances captured from the nares via high-resolution manometry and positioned with the proximal pH sensor inside the UES to prevent drying. With this placement method, the distal pH sensor ends up at a variable distance above the LES (due to only three catheter lengths being available for best fit in all patients) (see Figure 1). This variation from traditional reflux testing, where the distal pH sensor is placed 5 cm above the LES, was accepted as pharyngeal, and proximal data are more important in this patient group. Distal or "total" reflux was detected at the most distal impedance electrode, while proximal esophageal reflux was defined by events reaching one of the two uppermost electrode pairs within the esophageal body, just below the UES. Six or more events at these proximal esophageal impedance sensors just below the UES were called positive.[18] "Pharyngeal" reflux was defined by events reaching the hypopharyngeal impedance sensor electrode pairs, positioned within and just above the UES (see Figure 2). Two or more events at the hypopharyngeal pair was considered abnormal. The value for the number of pharyngeal events was chosen based on one event more than what was considered normative data in prior studies.[16,18]

Over the course of the 24-hour study, subjects were instructed to remain upright during the day and recumbent at night, and maintain their normal activities, including meals. Meal periods were documented via the data logger and excluded from analysis. All HEMII-pH tracings were reviewed with the assistance of a dedicated software package (*Bioview Analysis*, version 5.6.3.0; Sandhill Scientific Inc., Highlands Ranch, CO). The software-generated results for all exams were made more accurate through a detailed over-read by one of the senior authors (WC).

Several measures of reflux severity as determined by HEMII-pH were recorded for each subject, including the number and mean of distal and proximal esophageal acid events, the number and mean of distal, proximal, and pharyngeal impedance events, and bolus reflux exposure time (ie, percentage of study time spent in reflux). Previously established values, derived from normal volunteers, were

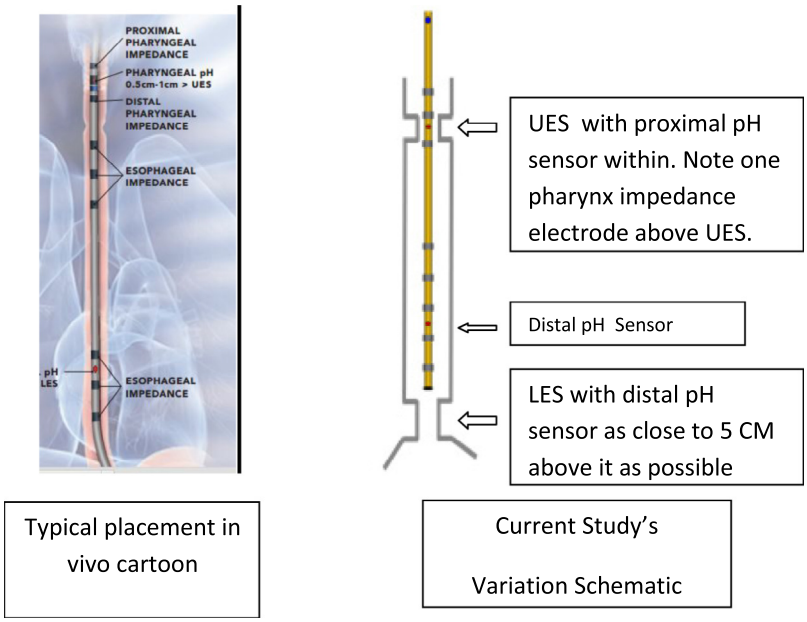

FIGURE 1. Example of MII LPR catheter placement in vivo (http://www.boucartmedical.be/wp-content/uploads/2015/04/lpr.pdf and Sandhill SCientific, Milwauke, WI). The current study's tracings would differ in that there would be only one "hypopharynx" impedance tracing as the second impedance electrode pair would be in the UES/proximal esophagus (as in the schematic next to the *in vivo* cartoon). This is done to avoid the drying of the upper pH sensor in the pharynx.

used to determine normal cutoffs for reflux episodes and exposure times.[16,18,19] Our testing interpretations did not distinguish between the upper two esophageal electrode pairs (detecting impedance 1−5 cm below the UES but not within or above the UES) and rather report both together as "proximal esophageal." Six or more events were designated as positive in the proximal esophageal electrodes to be conservatively higher than the 95th percentile value of 4, for the number of impedance events at 2 cm below the UES, reported in the Hoppo et al paper.[18]

Statistical analysis

Descriptive statistics were used to examine the demographic and clinical characteristics of the study cohort. Univariate analyses were performed to compare demographic and

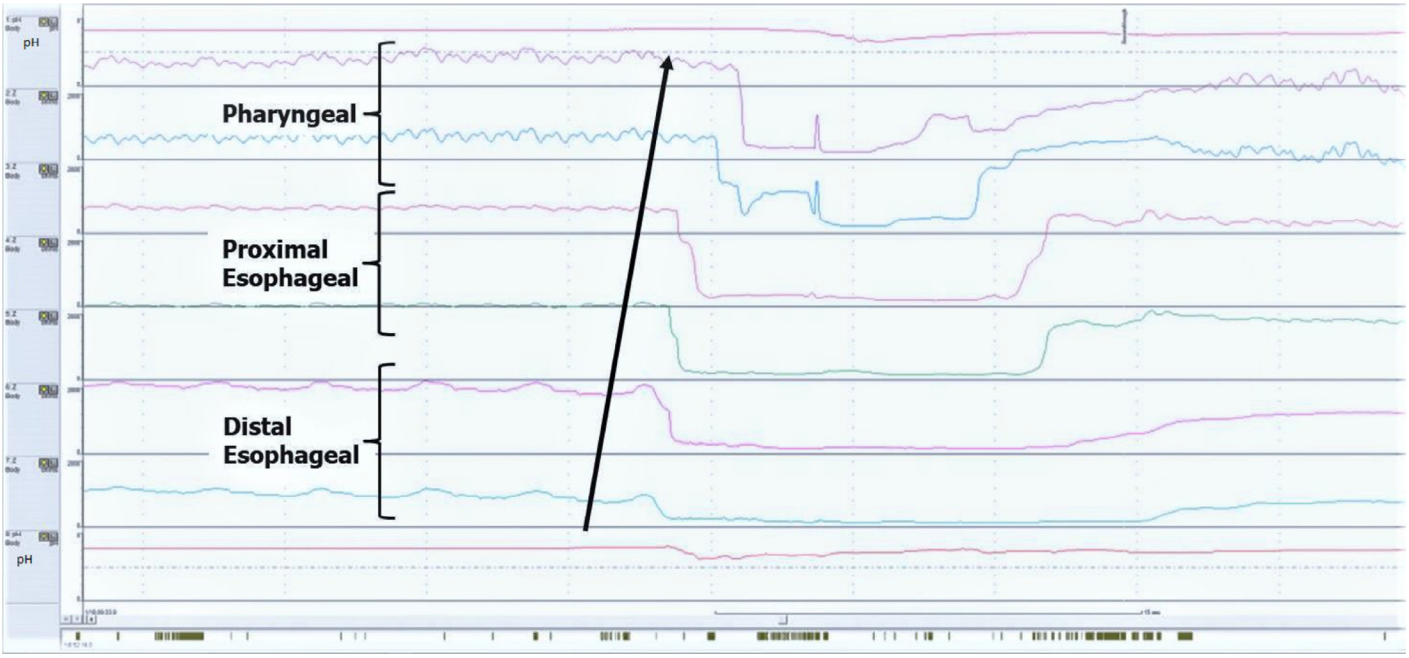

FIGURE 2. Example of a nonacidic pharyngeal reflux event. Note the sequential drop in impedance and that the liquid bolus moves in a retrograde fashion from above the LES to the pharyngeal impedance electrodes. Neither pH sensor detects an acidity below pH 4.

TABLE 1.
Baseline Demographic and Clinical Characteristics of the Study Cohort

Total Subjects, N	42
Female, n (%)	32 (76.2)
Mean age, y (range)	55.8 (24 – 82)
Mean BMI (±SD)	26.5 (±5.3)
Former smoker, n (%)	15 (35.7)
History of typical GERD symptoms, n (%)	24 (60.0)
Test performed on PPI, n (%)	12 (28.6)
Mean number of proximal esophageal impedance events, n (±SD)	23.3 (14.6)
Mean number of pharyngeal impedance events, n (±SD)	10 (±9.9)
Mean RSI score, n (±SD)	21.0 (±9.2)
Mean VHI score, n (±SD)	12.8 (±9.4)

Abbreviation: SD, standard deviation.

TABLE 3.
Comparison of HEMII-pH Findings Between Patients Tested While On and Off PPI Therapy

	On PPI	Off PPI	*P* Value
Acid-only events on pH catheter, n (±SD)			
Distal	7.4 (±9.8)	9.7 (±11.0)	0.52
Proximal	1.1 (±2.9)	0.3 (±0.8)	0.39
Impedance events on catheter, n (±SD)			
Distal	54.4 (±23.2)	40.8 (±25.3)	0.11
Proximal esophageal (near UES)	29.3 (±11.3)	20.9 (±15.2)	0.09
Pharyngeal	12.9 (±11.5)	8.9 (±9.2)	0.24

Abbreviation: SD, standard deviation.

clinical characteristics between patients who tested positive based on traditional impedance criteria for proximal reflux with patients who tested negative. Dichotomous variables were analyzed using Fisher's exact test, and continuous variables were analyzed using Student's *t* test. The student's *t* test was then used to compare the average number of acid and impedance reflux events measured in patients tested on and off PPI. Fisher's exact test was used to examine the relationships between testing positive for reflux using the traditional impedance criteria and testing positive using the newer pharyngeal and proximal esophageal criteria. The correlation between the number of pharyngeal events and distal or proximal reflux events detected on impedance were evaluated using Pearson's correlation coefficient.

RESULTS

As seen in Table 1, 32 (76.2%) of the subjects were female, and the mean age of the subjects was 55.8 years (range, 24−82). The mean BMI of the cohort was 26.5 (±5.3). Fifteen (35.7%) of the subjects reported a history of smoking, and 24 (60.0%) reported a history of typical GERD symptoms. Twelve (28.6%) of the subjects were tested while taking high-dose PPI therapy.

The mean RSI score reported in the cohort was 21, and the mean VHI score was 12.8. The mean number of proximal esophageal impedance events recorded was 23.3. The mean number of pharyngeal impedance events was 10.

Table 2 shows a comparison of patients who tested positive using traditional impedance criteria for proximal reflux (>31 events every 24 hours at 15 cm above the LES) and patients who tested negative (≤31 events every 24 hours at 15 cm above the LES). The two groups were statistically similar in all demographic and clinical characteristics, including their presenting RSI and VHI scores.

Whether a subject was tested on or off PPI did not have a significant impact on the number of acid or impedance reflux events measured (see Table 3).

When comparing the total number of pharyngeal reflux events with either distal esophageal events or proximal esophageal events, significant correlations were found ($r^2 = 0.731$, $P \leq 0.0001$, and $r^{22} = 0.777$, $P \leq 0.0001$, respectively). Analyses were then performed using previously published normative criteria for distal, proximal, and pharyngeal reflux events.

TABLE 2.
Comparison of Patients Who Tested Positive for Older, Proximal Impedance Reflux Criteria (>31 Events Every 24 Hours at 15 cm Above LES) Versus Those Who Tested Negative (≤31 Events Every 24 Hours at 15 cm Above LES)

	Older Criteria "Proximal" Reflux Positive (n = 13)	Older Criteria "Proximal" Reflux Negative (n = 29)	*P* Value
Female, n (%)	8 (61.5)	24 (82.7)	0.24
Mean age, y (±SD)	57.2 (±12.0)	55.1 (±15.4)	0.66
Mean BMI (±SD)	27.7 (±4.2)	26.0 (±5.6)	0.34
Former smoker, n (%)	3 (23.1)	12 (41.4)	0.31
Typical GERD history, n (%)	8 (61.5)	16 (55.2)	0.74
Total RSI score, n (±SD)	21.2 (9.4)	20.9 (9.3)	0.93
Total VHI score, n (±SD)	12.0 (11.7)	13.1 (8.5)	0.73

TABLE 4.
Results of HEMII-pH Testing Using Newer Proximal Esophageal Criteria, Pharyngeal Criteria, Breakthrough Acid Reflux, Reflux Symptom Correlation, and High-Resolution Manometry (HRM)

HEMII-pH and HRM Results	Abnormal
Positive by newer proximal esophageal criteria (≥6 events every 24 hours just below the upper esophageal sphincter)	92% (39/42)
Positive by pharyngeal reflux criteria (≥2 events every 24 hours above the upper esophageal sphincter)	81% (34/42)
Breakthrough acid reflux	0% (0/42)
Reflux symptom correlation	16.7% (7/42)
Abnormal high-resolution manometry	36% (13/36)
Ineffective esophageal motility (<60% effective swallows)	25% (9/36)
Hypotensive basal lower esophageal sphincter pressure (<10 mm Hg)	17% (6/36)

In total, 39 of 42 (92%) of patients tested positive when using a threshold of ≥6 full-column esophageal events in 24 hours, and 81% (34/42) of patients tested positive when using the pharyngeal criteria of ≥2 events above the UES in 24 hours (see Table 4). None of the subjects tested on PPIs demonstrated breakthrough acid. Reflux symptom correlation was poor as it was detected in only 16.7% of the total study cohort. Thirty-six percent of subjects had abnormal findings on manometry. As seen in the right two columns of Table 5, all patients who tested positive based on the traditional proximal impedance criteria also tested positive using these pharyngeal criteria ($P = 0.04$). However, of the patients who tested negative based on traditional criteria, 72% were found to be positive based on pharyngeal criteria.

Finally, when comparing patients who tested positive for reflux based on traditional distal esophageal impedance criteria (≥73 events every 24 hours) with those who tested negative (<73 events every 24 hours), it was found that traditional distal esophageal impedance criteria correlate well with traditional proximal impedance criteria (up to 15 cm above LES) ($P < 0.0001$). However, traditional distal esophageal criteria did not correlate well with pharyngeal criteria, as many patients who would test normal for reflux based on distal esophageal criteria would test positive based on this newer parameter ($P = 0.31$) (see Table 5).

DISCUSSION

Confirming the diagnosis of LPR in patients with atypical reflux symptoms can be challenging and has historically been limited to testing for acid reflux alone or using impedance catheters with dual pH that measure impedance up to 15 cm above the LES, thus missing events near or above the UES. We examined a cohort of patients with refractory LPR using hypopharyngeal-esophageal MII with dual pH-impedance (HEMII-pH) catheters that included impedance electrodes in the proximal esophagus and in the pharynx.

Based on the previously published cutoff of two or more pharyngeal impedance events being outside normative values in 24 hours, we found that most of our cohort (81%) tested positive for abnormal pharyngeal reflux despite their failure to improve with PPI therapy. In addition, we found that traditional impedance criteria for both distal and proximal esophageal reflux up to 15 cm above the LES were not reliable in excluding abnormal pharyngeal reflux. Our findings both support the use of HEMII-pH (with pharyngeal impedance sensors) in the evaluation of patients with refractory symptoms and highlights our current lack of understanding about what constitutes a true-positive HEMII-pH test.

Previously published data that used the aforementioned, earlier generation of impedance catheters (with dual pH and proximal impedance up to 15 cm above the LES) in suspected cases of LPR that failed high-dose, twice-daily PPI treatment demonstrated a rate of positive testing at 74% using the older technology.[20] In that study, positive tests that could explain the patient's persistent symptoms despite failing high-dose, twice-daily PPI therapy was defined as any of >31 impedance events in 24 hours at 15 cm above the LES, dysmotility on manometry, an elevated DeMeester score while tested on high-dose, twice-daily PPIs, or symptom correlation with

TABLE 5.
Comparison of HEMII-pH Reflux Events (Older Proximal Criteria and Pharyngeal) Between Subjects With Normal (Negative) and Abnormal (Positive) Distal Reflux (Defined as >73 Impedance Events Every 24 Hours Reaching 5 cm Above the LES)

	Normal Traditional Proximal Reflux (>31 Events at 15 cm Above LES),(%)	Abnormal Traditional Proximal Reflux (>31 Events at 15 cm Above LES), (%)	*P* Value	Normal Distal Reflux (n = 34)	Abnormal Distal Reflux (n = 8)	*P* Value
Abnormal traditional proximal reflux (>31 events at 15 cm above LES), (%)	-	-	-	5 (14.7)	8 (100)	<0.0001
Abnormal pharyngeal reflux (≥2 events), (%)	21 (72.4)	13 (100)	0.04	26 (76.5)	8 (100)	0.31

actual LPR events. This incidence is lower than the current study demonstrates (92% meeting proximal esophageal and 81% meeting pharyngeal criteria), suggesting that patients with true LPR are being missed using older technology and diagnostic criteria. Interestingly and in contrast to the prior study, no subject demonstrated an elevated DeMeester score/breakthrough acid reflux. This may be explained by the current study's cohort including many subjects tested off PPIs before empiric medication trials and not evaluating the DeMeester score as a positive criterion (due to the placement of the HEMII-pH probe, specifically targeting the proximal pH sensor within the UES). Additionally, relying on a proximal pH sensor only to detect proximal reflux appears to miss many subjects with nonacid LPR and the accompanying pepsin deposition that is likely causing their symptoms.[21,22]

Despite these findings, the missing link in understanding what truly designates an LPR diagnosis and then offering targeted therapy is knowing if these "above-normal" values for proximal esophageal and pharyngeal events are truly pathological for the individual patient. There likely exists variable concentrations of pepsin per reflux event and levels of individual sensitivity or tolerance to reflux events; diet, allergy, and environmental differences also exist between patients that might allow one individual to tolerate 10 pharyngeal nonacid reflux events, while another patient may have a chronic cough from only two events per 24 hours. Two recent studies evaluated the predictability of the newest HEMII-pH catheter as used in this study's cohort to predict LPR or cough symptom resolution after Nissen fundoplication. Seventy-eight percent of subjects in a study by Carroll et al had resolution of some of their LPR symptoms with 67% having complete resolution, and in a study by Hoppo et al, 81% of the subjects had complete resolution (the other 19% had partial resolution) of some of their cough symptoms.[15,23]

In the Carroll et al study, the Nissen failures were ultimately cured after other, subtle laryngeal pathologies that symptomatically mimicked the presentation of LPR, resolved after vocal fold augmentation. It appears that results from HEMII-pH and manometry, patient history, laryngeal exam that includes stroboscopy to rule out TVF abnormalities of closure pattern, and good clinical acumen are all involved with the diagnosis and treatment of LPR.[24,25]

A Pearson correlation was used to assess the relationship between the number of distal or proximal reflux events and the number of pharyngeal events. There were significant positive correlations between pharyngeal events and both distal and proximal reflux events. However, as demonstrated by the remainder of the results, when pharyngeal, distal, and proximal reflux events were dichotomized, abnormal distal or proximal reflux, as defined by traditional criteria, could not reliably predict abnormal pharyngeal reflux. We believe that this further strengthens the argument that traditional normative criteria for abnormal reflux are not sufficient to be used for diagnosing LPR, as defined by increased pharyngeal events.

Despite the ability to detect pharyngeal reflux, there is reasonable argument surrounding the reliability of the detection of these events due to issues with interrater and intrarater reliability.[16] When a patient refluxes, a swallow or belch can anecdotally accompany the event, making the pharyngeal event less clear. The proximal esophageal events just below the UES may prove more reliable than actual pharyngeal events. More work is required to evaluate this suspicion.

CONCLUSION

More subjects are identified with abnormal numbers of reflux events in the pharynx or near the UES using HEMII-pH than would have been identified using traditional distal esophageal pH or esophageal impedance/pH testing criteria. Using traditional GERD criteria to diagnose LPR appears inadequate. Further work to define and understand how many high proximal and pharyngeal impedance reflux events are pathological is needed.

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