Original Investigation

Antireflux Surgery in Patients With Chronic Cough and Abnormal Proximal Exposure as Measured by Hypopharyngeal Multichannel Intraluminal Impedance

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IMPORTANCE Chronic cough is a laryngeal symptom that can be caused by gastroesophageal reflux disease; however, treatment outcome has been difficult to predict because of the lack of an objective testing modality that accurately detects reflux-related cough.

OBJECTIVE To define the patterns of reflux and assess the outcome of antireflux surgery (ARS) in patients with chronic cough who were selected using hypopharyngeal multichannel intraluminal impedance (HMII).

DESIGN Review of prospectively collected data.

SETTING Tertiary care university hospital.

PARTICIPANTS Patients with chronic cough, which was defined as persistent cough (≥8 weeks) of unknown cause.

INTERVENTIONS Hypopharyngeal multichannel intraluminal impedance with a specialized catheter to detect laryngopharyngeal reflux and high-esophageal reflux (reflux 2 cm distal to the upper esophageal sphincter) and ARS.

MAIN OUTCOMES AND MEASURES Abnormal proximal exposure was defined as laryngopharyngeal reflux occurring 1 or more times per day and/or high-esophageal reflux occurring 5 or more times per day. The outcomes of ARS included symptomatic improvement.

RESULTS From October 2009 to June 2011, a total of 314 symptomatic patients underwent HMII. Of this population, 49 patients (15 men, 34 women; median age, 57 years) were identified as having chronic cough. Of the 49 participants, 23 of 44 patients (52%) had objective findings of gastroesophageal reflux disease, such as esophagitis. Abnormal proximal exposure was discovered in 36 of the 49 patients (73%). Of 16 patients with abnormal proximal exposure who subsequently underwent ARS, 13 patients (81%) had resolution of cough and 3 patients (19%) had significant improvement at a median follow-up of 4.6 months (range, 0.5-13 months).

CONCLUSIONS AND RELEVANCE A highly selective group of patients with idiopathic chronic cough may have abnormal proximal exposure to gastroesophageal reflux documented by HMII that would have not been detected with conventional pH testing. Thus, HMII is likely to improve the sensitivity of laryngopharyngeal reflux diagnosis and better elucidate those who will respond to antireflux surgery.

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Chronic cough lasting more than 8 weeks is a common entity that affects 8% to 12% of the adult population[1-3] and significantly affects quality of life.[4,5] Accumulating evidence has suggested that gastroesophageal reflux disease (GERD) is one of the causative factors in approximately 40% of patients with chronic cough.[6,7] Gastroesophageal reflux disease may cause cough through 2 primary mechanisms: vagal nerve-mediated cough reflex and direct exposure of gastric contents to the upper aerodigestive tract.[8,9] As recommended by the American College of Chest Physicians, an empirical trial of antisecretory medications, such as proton pump inhibitors, has been the initial step in the treatment of chronic cough regardless of whether patients have typical GERD symptoms[6]; however, a recent meta-analysis[10] did not support the diagnostic and therapeutic benefit of antisecretory medication in this setting. Furthermore, it has been suggested that non-acid reflux events likely play an important role in patients with chronic cough[6] and the pH of the refluxate may be irrelevant in patients who have a sensitized esophageal-bronchial reflex.[11,12]

Although a strong association between aspiration via proximal reflux events and certain pulmonary diseases, such as idiopathic pulmonary fibrosis, has been suggested,[13-15] few studies investigated the causal relationship between cough and laryngeal reflux and/or high-esophageal reflux in a highly curated group of patients with idiopathic chronic cough.[8] A dual-channel pH catheter traditionally has been used to evaluate proximal reflux events; however, a study[16] involving patients with chronic cough demonstrated that more than one-half of patients with positive pH test results did not respond to medical or surgical treatment, suggesting that solely a pH-based approach may be insufficient in the evaluation of these individuals.

Multichannel intraluminal impedance (MII) has been introduced as a promising tool to assess the proximity of reflux events regardless of pH. Recently, the normative data for laryngopharyngeal reflux (LPR) and high-esophageal reflux events (reflux 2 cm distal to the upper esophageal sphincter) were established using 24-hour hypopharyngeal MII (HMII) with a specialized impedance catheter.[17] From these data, we have established criteria to define abnormal proximal exposure (APE) as LPR of 1 or more events per day and/or high-esophageal reflux as 5 or more events per day and introduced these criteria into our practice to guide patient selection for antireflux surgery (ARS). The objectives of this study were to determine the patterns of reflux (ie, proximity, pH, composition, and duration) in patients with chronic cough using HMII and assess the outcome of ARS in patients selected for surgery based on the HMII criteria.

Methods

Study Design

This retrospective study was performed with the approval of the institutional review board of the University of Pittsburgh. Participants included symptomatic patients who were referred for the evaluation of GERD and/or LPR and had undergone esophageal objective testing including upper endoscopy, barium esophagram, high-resolution manometry (HRM), and HMII from October 1, 2009, to June 30, 2011. Chronic cough was defined as persistent cough of unknown cause that lasted for longer than 8 weeks. Patients with a known cause of cough, such as positive tuberculosis test, active smoking, use of an angiotensin-converting enzyme inhibitor, seasonal allergy, and pulmonary disease (eg, chronic obstructive pulmonary disease, asthma, and pulmonary fibrosis) were excluded. Antisecretory medications, such as proton pump inhibitors and H_2 receptor antagonists, were discontinued 10 days before HMII. Typical GERD symptoms were defined as heartburn and regurgitation, and atypical symptoms were defined as hoarseness, globus sensation, and throat clearing. Detailed demographic data (sex, age, body mass index [calculated as weight in kilograms divided by height in meters squared]), clinical data (medication, medical/surgical history, preoperative and postoperative symptoms, and duration of symptoms), and objective data (endoscopic/radiographic findings, manometric findings, and HMII) were obtained from medical records. On the basis of established normative data for LPR and high-esophageal reflux events for 24-hour HMII, APE was defined as LPR of 1 or more events per day and/or high-esophageal reflux of 5 or more events per day. Selected patients with APE subsequently underwent ARS, which was tailored on the basis of the preoperative esophageal motility status as measured by HRM, and the outcomes of ARS, including symptomatic improvement and antisecretory medication use, were retrospectively assessed.

Esophageal Objective Testing

Upper endoscopy and a barium esophagram were performed in all patients. Esophageal mucosal changes related to GERD, such as esophagitis and Barrett esophagus, were recorded. The severity of esophagitis was graded based on the Los Angeles Classification.[18] Barrett esophagus was suspected when the squamocolumnar junction was located proximal to the anatomic gastroesophageal junction. Four quadrant biopsy specimens were obtained every 2 cm across the length of suspected Barrett esophagus, and the diagnosis was confirmed histologically with the identification of goblet cells. The presence of proximal ectopic gastric mucosa (ie, inlet patch) was recorded, and these patients were excluded because of the potential for regional acid production and non-GERD-related LPR symptoms. A hiatal hernia, measured in centimeters, was considered present when the anatomic gastroesophageal junction was located proximal to the crural pinch.

High-resolution manometry was performed using a solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan; Sierra Scientific Instruments, Inc). Recently, bipositional HRM was introduced, in which 10 wet swallows were obtained in the supine position followed by 5 wet swallows in the upright position, to assess the positional effect on lower esophageal sphincter (LES) structure and function.[19] A defective LES was defined as an LES resting pressure of less than 5.0 mm Hg, total LES length of less than 2.4 cm, or intra-abdominal LES length of less than 0.9 cm based on previous studies.[20,21] Abnormal esophageal motility was defined as failed contractions of more than 20%, simultaneous

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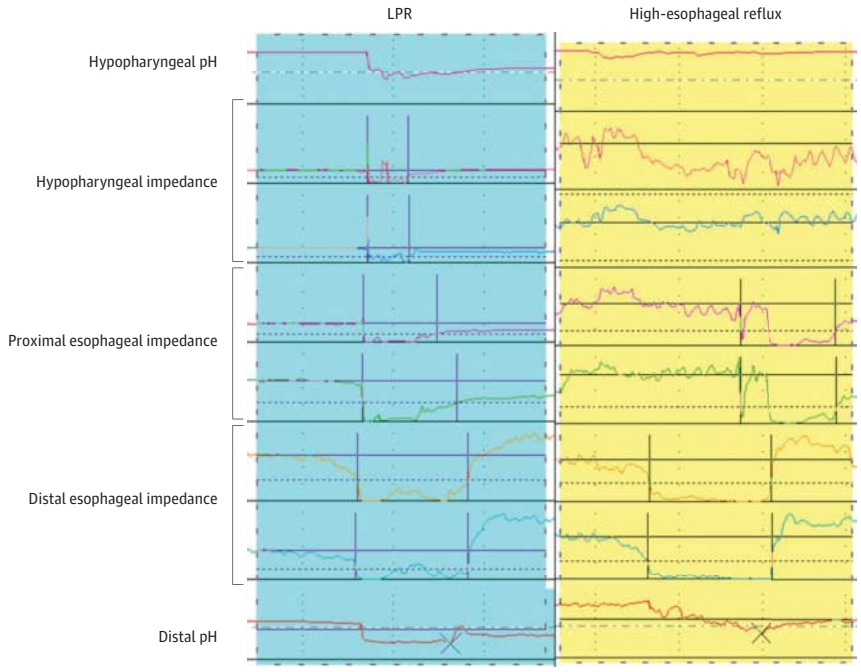
Figure 1. Typical Impedance Tracings of Laryngopharyngeal Reflux (LPR) and High-Esophageal Reflux



contractions of more than 20%, or low mean wave pressure amplitudes of less than 30 mm Hg.

Hypopharyngeal multichannel intraluminal impedance was performed using a specialized impedance catheter to directly measure LPR and high-esophageal reflux (catheter models CZAI-BL-54, -55, and -56; Sandhill Scientific Inc) as described previously.[22] The single-branch catheter has 2 sites for pH monitoring (hypopharynx and distal esophagus) and 2 pairs of impedance electrodes, each located in the hypopharynx, proximal esophagus, and distal esophagus. The catheter is placed based on the location of the upper esophageal sphincter under endoscopic guidance or on measurements obtained during manometry. After esophageal length is determined by manometry, catheter size is selected; this enables the distal pH probe to be positioned 5 cm (±1 cm) proximal to the upper border of the LES for the calculation of the DeMeester score. The catheter is connected to an ambulatory recording device. The impedance measurements, such as the proximity of reflux events, composition (liquid, gas, and mixed gas-liquid), and mean acid clearance time, were recorded for 24 hours. The DeMeester score was calculated using the established criteria, and a score greater than 14.7 was considered positive for the presence of GERD.[23] Meal times were excluded from the analysis. Patients were instructed to indicate symptoms and body position changes on the ambulatory recording device as well as to maintain a 24-hour diary of intake and symptoms, which were cross-referenced with the software output.

HMII Data Interpretation

Impedance data were analyzed using dedicated software (Bioview Analysis; Sandhill Scientific Inc) as described previously.[17] Briefly, a retrograde 50% fall in impedance from the mean baseline impedance between the 2 electrode pairs indicated the presence of liquid-only reflux. The mean was calculated from baseline impedance values measured 5 seconds before the decrease. An abrupt increase in impedance (gas) occurring during or immediately prior to liquid reflux indicated the presence of mixed gas-liquid reflux. The software automatically identified reflux events; however, every event was individually reviewed to exclude false-positive readings.

Definition of Proximal Reflux Events and Abnormal Proximal Exposure

An LPR event was considered present when retrograde bolus transit occurred across all ring sets and ultimately reached the hypopharynx (**Figure 1**). Acid and non-acid LPR were defined when both distal and hypopharyngeal pH dropped to less than 4 (acid) or both pH readings were greater than 4 (nonacid), respectively, in conjunction with an LPR event. A high-esophageal reflux event was present when reflux reached the impedance electrode pair 2 cm distal to the lower border of the upper esophageal sphincter but did not reach the hypopharyngeal electrode pair. Acid and nonacid high-esophageal reflux were defined when the distal pH dropped to less than 4 (acid) or was greater than 4 (nonacid), respectively, in conjunction with a high-esophageal reflux event. Based on the normative data established for LPR and high-esophageal reflux, APE was defined as LPR of 1 or more events per day and/or high-esophageal reflux as 5 or more events per day.

Symptom Association With Reflux Events

The association between cough episodes and reflux events was assessed using the Symptom-Association Probability (SAP) tool.[24] A 2-minute window following the initiation of each re-

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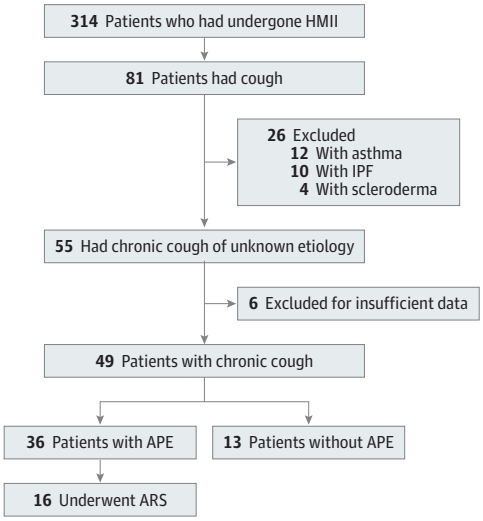
Figure 2. Flowchart of the Study



APE indicates abnormal proximal exposure; ARS, antireflux surgery; HMII, hypopharyngeal multichannel intraluminal impedance; and IPF, idiopathic pulmonary fibrosis.

flux event was used based on a study of the acid reflux-chest pain association,[25] and cough was considered "associated to a particular reflux event" if it occurred within this time window. The Fisher exact test was used to calculate the probability (*P* value) that the observed association between reflux and cough occurred by chance alone, and the SAP was calculated as (1.0 - *P* value) × 100%. The SAP values of 95% or greater were considered statistically significant.[24,26]

Statistical Analysis

Values are expressed as median (interquartile range). Because data were not normally distributed, statistical analysis was performed by means of the nonparametric Mann-Whitney test and Pearson χ^2 test using commercial software (SPSS, version 19; SPSS Inc), and $P < .05$ was considered statistically significant.

Results

Patient Demographics

Of 314 patients who underwent HMII at out institution from October 1, 2009, to June 30, 2011, 81 patients were identified as having chronic cough. Twenty-six of those patients were excluded because of a diagnosis of asthma (n = 12), idiopathic pulmonary fibrosis (n = 10), or scleroderma (n = 4), leaving 55 patients with chronic cough of unknown cause. Six patients were subsequently excluded because of insufficient data, and the remaining 49 patients (15 men, 34 women) were included in the final analysis (**Figure 2**). Median age and body mass index were 57 years (interquartile range, 50-63) and 28.4 (interquartile range, 25.1-32.8), respectively (**Table 1**). Nine patients (18%) had cough without any other symptoms, whereas 30 patients (61%) and 10 others (20%) had concomitant typical and atypical GERD

Table 1. Demographics for Patients With Chronic Cough

Characteristic	Patients, No. (%) (n = 49)
Sex	
Male	15 (31)
Female	34 (69)
Age, median (range), y	57 (50-63)
BMI, median (IQR)	28.4 (25.1-32.8)
Symptoms	
Isolated cough	9 (18)
Concomitant symptoms	
Typical	30 (61)
Atypical	10 (20)
Duration of clinical symptoms, y	
≤1	4 (10)
1-5	11 (27)
≥5	25 (62)
No data	9
Esophageal mucosal injury, No. (%)	23 (52)
LA grade	
A	9 (20)
B	4 (9)
C	3 (7)
D	1 (2)
Short BE	4 (9)
Esophageal stricture	2 (5)
No data	5
Hiatal hernia, No. (%)	24 (50)
PPI use	
Dependence	35 (81)
None	2 (5)

Abbreviations: BE, Barrett esophagus; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; LA, Los Angeles Classification; PPI, proton pump inhibitor.

Table 2. HMII Measurements

Characteristic	HMII Measurements, No. (%) (n = 49)
Abnormal proximal exposure	36 (74)
LPR events ≥1/d, No. (%) [range]	10 (20) [1-12]
High-esophageal reflux events ≥5/d, No. (%) [range]	35 (71) [5-32]
pH of refluxate, No.	
Acid	263 (63)
Nonacid	153 (37)
Composition of refluxate, %	
Liquid	215 (52)
Mixed gas-liquid	201 (48)
No. of total reflux events, median (range)	18 (9-26)
DMS, median (IQR)	5 (1.5-15.7)
Positive	14/49 (28)
Negative	35/49 (71)
Symptom association probability	
Positive	11/43 (26)
Positive SAP in DMS	
Positive	3/14 (21)
Negative	7/35 (20)

Abbreviations: DMS, DeMeester score; HMII, hypopharyngeal multichannel intraluminal impedance; IQR, interquartile range; LPR, laryngopharyngeal reflux; SAP, Symptom Association Probability.

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Table 3. Comparison of Patients With vs Without APE

Characteristic	Patients, No. (%)		P Value
	With APE (n = 36)	Without APE (n = 13)	
Sex			
Male	11 (31)	4 (31)	
Female	25 (69)	9 (69)	
Age, median (range), y	58 (51-65)	54 (47-61)	.19
BMI, median (IQR)	28.5 (26.0-33.9)	26.5 (23.1-30.5)	.17
Symptoms, No.			
Isolated cough	6 (17)	1 (8)	
Concomitant typical symptoms	30 (83)	8 (62)	
Duration of symptoms, y			
≥1	2 (7)	2 (18)	
1-5	6 (21)	4 (36)	
≥5	21 (72)	5 (45)	
No data	7	2	
Esophageal mucosal injury	19 (56)	3 (33)	
Hiatal hernia	18 (50)	6 (46)	
PPI dependence	24 (83)	11 (92)	
No data	7		
Total reflux events	21 (15-27)	7 (5-14)	<.001[a]
DeMeester score, median (IQR)	6.6 (2.4-19.8)	1.7 (0.8-12.2)	.003[a]
Positive	12/36 (33)	2/13 (15)	
Negative	24/36 (67)	11/13 (85)	
Mean acid clearance time, s	84 (46-183)	72 (0-191)	.28
Symptom association probability			
Positive	8 (25)	3 (27)	.98
Supine HRM	33	13	
Esophageal motility			
Abnormal	14 (42)	5 (38)	
Normal	19 (58)	8 (62)	

Abbreviations: APE, abnormal proximal exposure; BMI, body mass index; HRM, high-resolution manometry; IQR, interquartile range; PPI, proton pump inhibitor.

[a] Significant at $P < .05$.

symptoms, respectively. Typical symptoms were more likely to be responsive to proton pump inhibitor therapy; however, cough was persistent despite antisecretory therapy. Data on duration of cough were available for 40 patients. Of these, cough had been present for more than 1 year in 36 patients (90%), and 25 patients (62%) had had cough for more than 5 years. Objective findings of GERD, such as esophageal mucosal injury, were identified in 23 of 44 patients with reported data (52%), and 24 patients had a hiatal hernia.

Patterns of Reflux as Measured by HMII

Abnormal proximal exposure was identified in 36 patients (73%) with chronic cough; 10 patients (20%) and 35 patients (71%) had an abnormal number of LPR events (median, 2; range, 1-12) and high-esophageal reflux events (median, 8; range, 5-32), respectively. However, the total number of reflux events was normal in most patients (median, 18; interquartile range, 9-26), and 35 of 49 patients (71%) had a negative DeMeester score. Nonacid APE events were common (153 of 416 [37%]), and these events would not have been detected with conventional pH testing. There was no significant difference in the composition of LPR and high-esophageal reflux events. There was a positive SAP score in 11 patients (26%) patients, and there was no significant difference in SAP positivity between patients with a positive DeMesteer score and those with a negative score (3 [21%] vs 7 [20%], respectively) (**Table 2**).

Patients With vs Without APE

Sex distribution, age, and body mass index were comparable between patients with (n = 36) and those without (n = 13) APE (**Table 3**). Although concomitant typical GERD symptoms were common in both groups, patients with APE were more likely to have isolated cough compared with those without APE. Although the finding was not statistically significant, patients with APE had a higher prevalence of long-term cough (>5 years), objective findings of GERD such as esophageal mucosal injury, and a defective LES than did patients without APE. The total number of reflux events and DeMeester score were significantly higher in patients with APE. Approximately 40% of patients in both groups had abnormal esophageal motility (14 [42%] patients with APE and 5 [38%] of those without APE), and there was no significant difference in the mean acid clearance time between the groups. The SAP positivity was comparable between the groups ($P = .98$). Bipositional HRM demonstrated that the diagnostic yield of defective LES detection was increased from 60% to 80% in patients with APE compared with 44% to 67% in those without APE (**Table 4**).

Outcomes of ARS

Of 36 patients with APE, 16 patients subsequently underwent ARS including Nissen (n = 10), Dor (n = 2), Toupet fundoplication (n = 1), and esophagojejunostomy (n = 3) (**Table 5**). Partial fundoplication (Dor or Toupet) was selected for patients

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Table 4. Comparison of Bipositional HRM in Patients With vs Without APE

Bipositional HRM	With APE, No. (%)		Without APE, No. (%)	
	Supine (n = 30)	Upright (n = 30)	Supine (n = 9)	Upright (n = 9)
Defective LES	18 (60)	24 (80)	4 (44)	6 (67)
Hypotensive LES	2 (7)	10 (33)	1 (11)	3 (33)
Short LES	18 (60)	22 (73)	3 (33)	4 (44)
Short intra-abdominal LES	11 (37)	13 (43)	2 (22)	3 (33)

Abbreviations: APE, abnormal proximal exposure; HRM, high-resolution manometry; LES, lower esophageal sphincter.

with severe esophageal motility disorder, defined as failed swallows of more than 80%, and esophagojejunostomy was performed in 3 patients with complicated GERD who had had prior fundoplication that failed. Of the remaining 20 patients who did not undergo ARS, 12 patients were scheduled or recommended for ARS that had not been performed during this study, 6 patients had no objective findings of GERD except APE, and 2 patients with eosinophilic esophagitis (n = 1) and nutcracker esophagus (n = 1) were recommended to receive treatment for these diseases before consideration of ARS. Of 16 patients who had undergone ARS, 6 had a positive preoperative DeMeester score and 5 had a positive SAP score; 2 patients had both a positive DeMeester score and a positive SAP score. During a median follow-up of 4.6 months (range, 0.5-13 months), 13 patients (81%) had resolution of cough and 3 patients (19%) had a significant improvement (partial resolution). Of 3 patients who had partial resolution, SAP and DeMeester scores were both negative in 1 patient and both positive in 1 patient, and 1 patient had a positive SAP but negative DeMeester score. All patients discontinued the use of antisecretory medication after ARS except one individual, who had a partial response to ARS and required occasional antacid medication because of heartburn despite an endoscopically and radiographically normal appearance of fundoplication. Symptoms in all patients responded to ARS.

Table 5. Antireflux Surgery and Its Outcomes in Patients With Abnormal Proximal Exposure

Characteristic	Patients Who Had Undergone ARS, No. (n = 16)
Type of ARS	
Nissen	10 (63)
Dor	2 (13)
Toupet	1 (6)
Esophagojejunostomy	3 (19)
Follow-up, median (range) [IQR], mo	4.6 (2.0-8.4) [0.5-13.0]
DMS	
Positive	6 (38)
Negative	10 (62)
Symptom association probability	
Positive	5 (31)
Negative	11 (69)
Resolution of cough, No. (%)	13 (81)
Significant improvement, No. (%)	3 (19)
DMS, preoperative	
Positive	1 (33)
Negative	2 (66)
SAP	
Positive	2 (66)
Negative	1 (33)
No response to ARS	0

Abbreviations: ARS, antireflux surgery; DMS, DeMeester score; IQR, interquartile range; SAP, Symptom Association Probability.

Discussion

The causal relationship between cough and LPR has been poorly understood. Given that cough receptors are expressed on sensory neurons in the laryngopharynx and the airway,[27,28] direct exposure of gastric contents to the upper aerodigestive tract can activate cough receptors, potentially leading to persistent cough. Furthermore, it has been demonstrated[29] that as few as 3 episodes of LPR per week can cause severe laryngeal inflammation and injury, suggesting that even a very small number of LPR events can cause chronic cough, especially if cough receptors (neural pathways of cough) are already sensitized.

In the present study, we used HMII to evaluate LPR and high-esophageal reflux; APE was commonly observed in this population, and the presence of APE appears to be associated with long-standing GERD with severe LES dysfunction. Interestingly, many patients with APE had a normal number of total reflux events and a negative DeMeester score. These data were compatible with previous studies, which have not found an increased number of reflux events in patients with chronic cough compared with healthy individuals.[11,30,31] These data suggest that a "pH-centric" approach may be insufficient to evaluate patients with chronic cough, and actual tracing of reflux events would be optimal to assess their proximity and association with cough episodes.

It is preferable to document the correlation between clinical symptoms and reflux events to guide successful treatment; however, the assessment of association between cough episodes and reflux events has been challenging. The efficacy of SAP with a 2-minute time window to assess the temporal association between reflux and cough has been suggested[32]; however, the 2-minute time window was originally determined on the basis of reflux-chest pain association, and the optimal time window for cough remains unclear. Previous studies[8,11,32,33] have demonstrated that the currently used data logger and symptom diary to record cough episodes tend to underreport the occurrence of cough episodes, probably reducing the sensitivity of SAP. To more accurately assess the timing and number of cough episodes, some novel recording systems, including ambulatory esophageal pressure monitoring (manometry)[11,32-34]

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and cough sound recording,[12] have been investigated. In a study involving 100 patients with chronic cough, Blondeau and colleagues[32] used ambulatory manometry for objective cough monitoring and demonstrated that the SAP was increased from 11% (patient-reported cough events) to 36% (manometry system). In the most recent study using an ambulatory cough sound recording device, Smith and colleagues[12] demonstrated that 48% of patients with cough had a positive SAP score for reflux-associated cough, and the SAP-positive patients had an increased cough reflex sensitivity but were unlikely to have esophagitis or proximal reflux, suggesting that SAP-positive patients have a sensitized esophageal-bronchial reflex. Conversely, in a study evaluating pharyngeal reflux using MII, Patterson and colleagues[8] demonstrated that 27% of patients with either unexplained cough (n = 17) or asthma (n = 19) had a positive SAP, and the SAP-positive patients were more likely to have pharyngeal reflux events compared with SAP-negative patients (5 [2-8] vs 2 [0-4]); $P < .05$). In the present study, a positive SAP score was not associated with the presence of APE or improved outcomes of ARS. These data suggest that the role of SAP in cough remains unclear, and further studies are required to determine the optimal setting of SAP for cough. There is a need for more specific, simple criteria to select patients who likely respond to the treatment.

Proton pump inhibitors increase the pH of gastric contents but do not address the impaired barrier function at the gastroesophageal junction, and patients may continue to have nonacid or weakly acidic reflux, likely resulting in the conflicting outcomes of medical therapy in this setting. Antireflux surgery is effective to eliminate all types of reflux by anatomically reconstructing the gastroesophageal valve, potentially leading to the superior treatment outcomes with medical therapy. A systematic review[35] involving 13 studies assessing the role of ARS in patients with reflux-associated cough demonstrated that response rates ranged from 60% to 100%, and overall surgical treatment for cough was less successful than that for typical GERD. In most studies, patients were evaluated using pH testing, potentially causing inadequate patient selection for ARS. In the present study, patients were selected on the basis of the presence of APE regardless of whether there was a positive DeMeester score or a positive SAP score, and all patients had either complete or partial symptomatic response to ARS, although the follow-up period was short. Interestingly, neither the DeMeester score nor the SAP score affected outcomes, suggesting that APE may serve as an independent predictor of successful response to ARS in a subgroup of patients with chronic cough.

There are some limitations to this study. Objective symptom assessment using a validated questionnaire was not performed. However, patients were thoroughly interviewed at every clinic visit, and the preoperative and postoperative symptoms were precisely recorded in the medical record. The study population was highly selected, which may have led to a sampling bias. However, this study highlights that a specific subpopulation of patients with unexplained chronic cough may be associated with APE, which could aid in selection for successful ARS. The SAP was calculated based on patient-reported cough events and may be underestimated. Finally, the sample size was small and the follow-up period was short. Because cough reflex hypersensitivity is a key feature in most patients with chronic cough and may be persistent even after reflux is eliminated,[27] a prospective, controlled study with long-term follow-up is required to evaluate the benefit of our criteria for APE in patient selection.

Conclusions

Based on the retrospective analysis of a highly selective group of patients with chronic cough, chronic cough may be associated with APE as measured by HMII, and these patients are likely to respond to ARS. Patients with APE are more likely to have objective findings of GERD, a long duration of symptoms, and defective LES compared with those without GERD. The SAP tool appears to be inadequate to predict the presence of APE or select patients who likely respond to ARS. The presence of APE could be an independent factor for patient selection, and a prospective, controlled study with long-term follow-up is required to validate our criteria.

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Invited Commentary

Antireflux Surgery, a Cough Medicine Difficult to Swallow for Most Physicians

Marco G. Patti, MD

This study by Hoppo and colleagues[1] stresses many important aspects of the diagnosis and treatment of patients with chronic cough of unknown origin.

- Some of these patients have abnormal proximal reflux of gastric contents.
- For some of these patients cough is the primary symptom, and they do not experience typical symptoms of gastroesophageal reflux disease, such as heartburn or regurgitation. Therefore, testing for reflux is of paramount importance to detect abnormal proximal reflux and establish an association between symptoms and episodes of reflux.
- Although an empirical trial with proton pump inhibitors is the initial approach followed by most primary physicians, it is mostly useless since it fails in most patients from both a diagnostic and therapeutic point of view.
- Conventional pH testing may fail to detect the proximal extent of the refluxate when it is weakly acid or nonacid. Hypopharyngeal multichannel intraluminal impedance is the most sensitive test available today.
- Once a cause-and-effect relationship between reflux and respiratory symptoms has been established, antireflux surgery should be the primary form of treatment. Impedance technology has in fact shown that proton pump inhibitors just change the pH of the gastric refluxate, but reflux still occurs through an incompetent lower esophageal sphincter. As shown in this study in a highly selected group, a properly performed fundoplication stops instead any type of reflux, resolving or improving symptoms in most patients.

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It is time that the medical community recognizes that there is a link between the esophagus and the lung. Until new medications that restore the competence of the lower esophageal sphincter are available, antireflux surgery should be considered in carefully studied and selected patients with respiratory symptoms secondary to reflux.

ARTICLE INFORMATION

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