ORIGINAL ARTICLE

Proximal Reflux as a Cause of Adult-Onset Asthma

The Case for Hypopharyngeal Impedance Testing to Improve the Sensitivity of Diagnosis

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Objectives: To determine the patterns and proximity of reflux events in patients with adult-onset asthma (AOA) using hypopharyngeal multichannel intraluminal impedance (HMII) and to assess outcomes of antireflux surgery (ARS) in patients with AOA.

Design: Retrospective review of prospectively collected data.

Setting: University hospital.

Patients, Interventions, and Outcomes: All patients with AOA referred to our testing center underwent HMII, and those with abnormal proximal exposure, defined as laryngopharyngeal reflux at least once a day and/or high esophageal reflux at least 5 times a day, subsequently underwent ARS.

Results: From October 1, 2009, through June 30, 2011, a total of 31 patients with AOA (4 men and 27 women; mean age, 53 years) underwent HMII. Of 27 patients with available information, 11 (41%) had objective evidence of reflux disease. Nineteen patients (70%) had concomitant typical reflux symptoms. Despite a frequently negative DeMeester score, abnormal proximal exposure, which occurred in the upright position, was observed in 19 patients (70%). Of 20 patients who subsequently underwent ARS, asthma symptoms improved in 18 (90%), and 6 of them discontinued or reduced pulmonary medications at a mean (range) follow-up of 4.6 (0.6-15.2) months. Pulmonary function test results before and after ARS revealed that of 5 patients, 4 (80%) had improvement of the forced expiratory volume in the first second of expiration and/or the peak expiratory flow rate, which correlated with symptomatic improvement.

Conclusions: Adult-onset asthma is associated with abnormal proximal exposure of the aerodigestive tract to refluxate; these patients respond to ARS despite negative pH test results. Patients with AOA should undergo testing with HMII because they would not be detected with conventional pH testing.

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GASTROESOPHAGEAL REflux disease (GERD) is the most common esophageal disorder in Western countries.[1] Although patients with GERD typically present with heartburn and regurgitation, many patients also report atypical (extraesophageal) symptoms, such as globus sensation, hoarseness, and throat clearing, and respiratory symptoms, such as cough and shortness of breath. Accumulating evidence suggests a strong association between GERD and pulmonary diseases, including adult-onset asthma (AOA). The prevalence of GERD in patients with asthma has been reported to range from 30% to 90%.[2-5] On this basis, guidelines[6] for the treatment of asthma issued from the National Institutes of Health recommended that evaluation for the presence of GERD be considered in patients with poorly controlled asthma.

The relationship between asthma and GERD is complex, and 3 primary mechanisms have been suggested for GERD-induced AOA; first, acid exposure to the distal esophagus can stimulate vagal nerve afferent fibers, resulting in bronchoconstriction and the development and/or exacerbation of asthma.[7-9] Second, direct exposure of the trachea, bronchi, and lungs via microaspiration may induce bronchoconstriction and asthma. Finally, attenuation of the pharyngo-cricopharyngeal reflex may result in the inability of the upper esophageal sphincter to contract appropriately in the face of reflux events, thereby enabling direct exposure.[7,10-12] Numerous studies have demonstrated the potential pulmonary benefits of GERD treatment in asthmatic patients.[13-19] However, the outcome of treatment remains unpredictable because current testing measures used to diagnose GERD-caused asthma have poor sensitivity.[20,21] In this

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context, it is important to consider that chronic asthma and its attendant cough and pulmonary hyperinflation can result in the development of GERD, and this may lead to an ineffective therapeutic response in the treatment of asthma with antireflux surgery (ARS).

Recently, our group established normative data for laryngopharyngeal reflux (LPR) and high esophageal reflux using 24-hour hypopharyngeal multichannel intraluminal impedance (HMII).[22] Laryngopharyngeal reflux and high esophageal reflux events, collectively referred to as proximal reflux, were found to be rare in healthy subjects. On the basis of the normative data for HMII, abnormal proximal reflux was considered present when patients had LPR at least once per day and/or high esophageal reflux at least 5 times per day, and we introduced these criteria into our practice. The objective of this study was to determine the pattern and proximity of reflux events in patients with AOA using HMII. In addition, the outcome of ARS in patients with AOA who were selected on the basis of the presence of abnormal proximal exposure was assessed.

METHODS

STUDY DESIGN

This retrospective review was performed with the approval of the institutional review board of the University of Pittsburgh. Patients with AOA were extracted from the entire cohort of patients with typical and/or atypical GERD symptoms who had undergone HMII for the evaluation of GERD and/or LPR symptoms from October 1, 2009, through June 30, 2011. Antisecretory medications, such as proton pump inhibitors (PPI) and H2 antagonists, were discontinued 10 days before HMII. Adult-onset asthma was defined when patients with respiratory symptoms such as wheezing, cough, and shortness of breath were diagnosed with asthma as an adult (≥20 years old) and used at least 1 asthma medication, such as a bronchodilator or corticosteroid, at the time of evaluation for GERD. Patients who had an additional pulmonary diagnosis in addition to asthma (eg, idiopathic pulmonary fibrosis or scleroderma) were excluded. Detailed demographic data (sex, age, and body mass index [calculated as weight in kilograms divided by height in meters squared]), clinical data (medication, medical history, surgical history, preoperative and postoperative symptoms, and PPI dependence), and objective data (HMII and high-resolution manometry measurements and findings from the radiogram, endoscopy, and preoperative and postoperative pulmonary function testing) were obtained from the medical record. Typical symptoms included heartburn and regurgitation, and atypical symptoms included hoarseness, globus sensation, throat clearing, and cervical dysphagia. On the basis of HMII measurements, selected patients subsequently underwent ARS using our criteria.[22] The outcomes of ARS were assessed and were compared between patients with positive and negative DeMeester scores. The outcome measures of ARS included symptomatic improvement, elimination of antisecretory medications, and reduction or discontinuation of asthma medications. Pulmonary function test results before and after ARS, including the forced expiratory volume in the first second of expiration and the peak expiratory flow rate, were compared.

ESOPHAGEAL OBJECTIVE TESTING

Upper Endoscopy and Esophagram

All patients underwent endoscopic and/or radiographic evaluation of the upper gastrointestinal tract. Any esophageal mucosal changes, such as esophagitis or suspected Barrett esophagus, were recorded. The severity of esophagitis was graded using the Los Angeles classification.[23] Barrett esophagus was suspected when the squamocolumnar junction was variegated and located proximal to the anatomic gastroesophageal junction, and the diagnosis of Barrett esophagus was confirmed histologically. The presence of hiatal hernia was evaluated endoscopically and radiographically.

High-Resolution Manometry

High-resolution manometry was performed using a solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan; Sierra Scientific Instruments, Inc) to evaluate the function of the upper esophageal sphincter, esophageal body, and lower esophageal sphincter (LES). We introduced bipositional high-resolution manometry, in which 10 wet swallows (5 mL of water per swallow) were obtained in the supine position followed by 5 wet swallows in the upright position, to assess positional effects on LES function and structure. A defective LES was defined as either an LES pressure of less than 5.0 mm Hg, total LES length of less than 2.4 cm, or intra-abdominal length of less than 0.9 cm on the basis of established criteria.[24] Abnormal esophageal motility was defined as failed contractions of greater than 20%, simultaneous contractions of greater than 20%, or low mean wave pressure amplitudes of less than 30 mm Hg.

24-Hour HMII

Hypopharyngeal multichannel intraluminal impedance was performed using a specialized impedance catheter configured to detect acid and nonacid LPR (CZAI-BL-54, -55, or -56; Sandhill Scientific, Inc). This catheter has 2 pH probes (hypopharynx and distal esophagus) and 2 pairs of impedance electrodes each in the hypopharynx, proximal esophagus (2 and 4 cm distal to the upper esophageal sphincter), and distal esophagus (3 and 5 cm proximal to the gastroesophageal junction). On the basis of manometric measurements of esophageal length, the optimal length of the impedance catheter was selected so that the distal pH probe was positioned 5 cm (±1 cm) proximal to the LES[22]; the hypopharyngeal pH probe was positioned precisely at 0.5 cm proximal to the cricopharyngeal muscle under endoscopic visualization. This positioning protocol ensures that the most proximal impedance ring set is located within the hypopharynx. The most proximal *esophageal* ring set is located 2 cm distal to the lower border of the cricopharyngeus muscle. The DeMeester score was calculated using the established criteria,[25] and a score greater than 14.7 was considered positive for pathologic acid reflux. The catheter was attached to an ambulatory recording device, and the total testing period was 24 hours. Composition (liquid, gas, or mixed), proximity, and duration of reflux events were recorded.

HMII DATA INTERPRETATION AND DEFINITION OF PROXIMAL REFLUX EVENTS

Data were uploaded from the recording device and analyzed with dedicated software (Bioview Analysis; Sandhill Scientific, Inc). The details of data interpretation have been de-

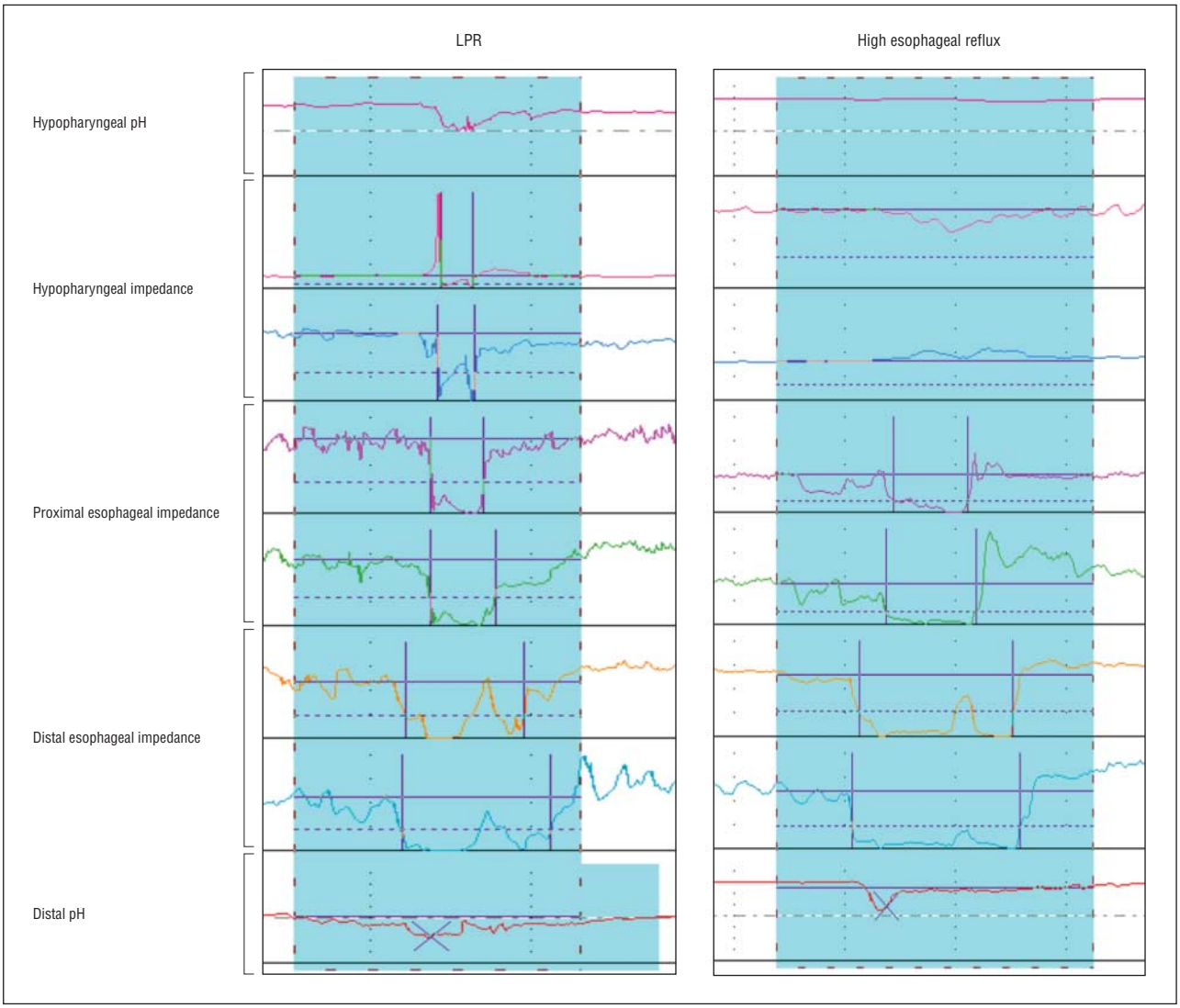

Figure 1. Representative impedance tracings of laryngopharyngeal reflux (LPR) and high esophageal reflux. Left, distal pH decreased to less than 4, and retrograde bolus transit reached the hypopharynx. There was a hypopharyngeal pH decrease, but it remained greater than 4, indicating acid (distal) to nonacid (hypopharyngeal) LPR secondary to mixing with saliva. Right, distal pH decreased no less than 4, and retrograde bolus transit reached the impedance electrode pairs 2 cm distal to the cricopharyngeus muscle but did not reach pharyngeal electrodes, indicating nonacid (distal) high esophageal reflux.

scribed in detail previously.[22] Briefly, a liquid-only reflux event was defined as a retrograde 50% fall in impedance from mean baseline impedance between the 2 electrode pairs, whereas mixed liquid-gas reflux was defined as an abrupt increase in impedance (gas) occurring during or immediately before liquid reflux. An LPR event was considered present when retrograde bolus transit reached the hypopharynx, regardless of whether there was a change in pH. On the basis of pH in the hypopharynx and distal esophagus, an LPR event was categorized into 2 groups: acid LPR (both pH <4) and nonacid LPR (both pH >4). A high esophageal event was defined as reflux that reached the electrode pairs 2 cm distal to the cricopharyngeus muscle but did not reach the hypopharyngeal ring set (**Figure 1**). On the basis of pH in the distal esophagus, a high esophageal event was categorized into 2 groups: acid and nonacid high esophageal reflux. Abnormal proximal exposure was considered present when patients had LPR at least once per day and/or high esophageal reflux at least 5 times per day. Patients with AOA were offered ARS if they fulfilled the HMII criteria for abnormal proximal exposure.

DATA ANALYSIS

Values were expressed as a median (range) or mean (SD). Because data were not normally distributed, statistical analysis was performed with the nonparametric Mann-Whitney test and Pearson χ^2 test using SPSS, version 19 (SPSS, Inc). $P < .05$ was considered significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS AND ESOPHAGEAL TESTING IN PATIENTS WITH AOA

From October 1, 2009, through June 30, 2011, a total of 314 symptomatic patients underwent HMII for the evaluation of GERD and/or LPR symptoms. Of 314 patients evaluated, 31 (9.9%) met criteria for AOA; 4 were excluded because of insufficient data or additional pulmo-

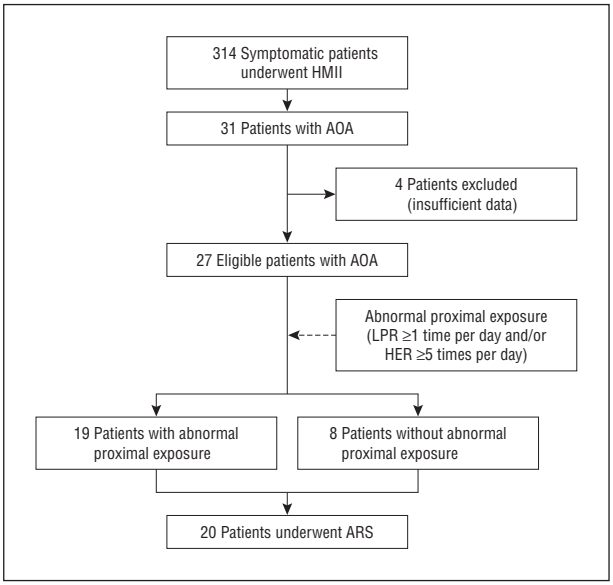

Figure 2. Flowchart of patient selection. AOA indicates adult-onset asthma; ARS, antireflux surgery; HER, high esophageal reflux; HMII, hypopharyngeal multichannel intraluminal impedance; and LPR, laryngopharyngeal reflux.

nary diagnoses (**Figure 2**). Mean (range) age and body mass index were 53 (23-74) years and 29.7 (21.0-42.5), respectively. Before surgical intervention, control of asthma symptoms was poor, with 22 patients (81%) reporting persistent wheezing, cough, and/or shortness of breath despite medical treatment using both pulmonary and antisecretory medications. Nineteen patients (70%) had concomitant typical GERD symptoms that were responsive to PPI (**Table 1**). Although 11 patients (41%) had endoscopic findings of GERD, such as esophagitis and Barrett esophagus, the overall severity of esophageal injury was mild. Hiatal hernia was found in 15 patients (56%). Despite suspicious findings of GERD, 19 patients (70%) had a normal DeMeester score. On the basis of high-resolution manometry evaluation, the LES became defective in 4 patients (15%) when they were moved from the supine to upright position.

PROXIMITY AND PATTERNS OF EXPOSURE IN PATIENTS WITH AOA

On the basis of HMII measurements, a total of 28 LPR events and 242 high esophageal events were recorded in patients with AOA (**Table 2**). Abnormal proximal exposure was identified in 19 patients with AOA (70%) and included 9 (33%) with LPR (median [interquartile range] number of events, 2 [2-5]) and 17 (63%) with high esophageal reflux (14 [9-15]) (Table 1). Both LPR and high esophageal events occurred almost exclusively in the upright position. The proportions of LPR and high esophageal nonacid events were 20% and 36%, respectively. Laryngopharyngeal reflux events were more often liquid only, and high esophageal reflux events were equally divided between liquid only and mixed liquid and gas (Table 2). Correlation between asthma symptoms and reflux events as measured by HMII was consistently low in both groups (median [interquartile range], 8.0% [0%-21.5%] vs 0% [0%-9.25%]; $P = .48$) (**Table 3**). Total acid exposure time was significantly longer in patients with abnormal proximal exposure (median, 36.4 seconds vs 9.1 seconds; $P = .045$), whereas acid clearance time was similar between the groups (111 seconds vs 85 seconds; $P = .73$). The number of total reflux events and the DeMeester score were significantly higher in patients with abnormal proximal exposure compared with those without abnormal proximal exposure.

Mean age, body mass index, and distribution of concomitant typical/atypical GERD symptoms were no dif-

Table 1. Demographic Characteristics of 27 Patients With AOA

Variable	Value
Age, mean (range), y	53 (23-74)
Sex, No.	
Male	4
Female	23
BMI, mean (range)	29.7 (21.0-42.5)
Preoperative control of asthmatic symptoms, No. (%)	
Poor	22 (81)
Good	5 (19)
Concomitant GERD symptoms, No. (%)[a]	
Typical	19 (70)
Atypical	10 (37)
PPI dependence, No. (%)	21 (78)
Esophageal mucosal injury, No. (%)	11 (41)
Esophagitis, LA classification, No.	
A	4
B	2
C	3
D	0
Barrett esophagus, No.	3
Hiatal hernia, No. (%)	15 (56)
DMS, mean (range)	12.5 (0.8-89.7)
Positive DMS (>14.7), No. (%)	8 (30)
Esophageal motility disorder[b]	
Normal	18
Abnormal	8
Defective LES, No. (%)	
LESP <5 mm Hg	
Supine	1/20 (5)
Upright	7/20 (35)
LESL <2.4 cm	
Supine	8/20 (40)
Upright	12/20 (60)
IAL <0.9 cm	
Supine	6/20 (30)
Upright	10/20 (50)
Total	
Supine	10/20 (50)
Upright	13/20 (65)
Abnormal proximal exposure, No. (%)	19 (70)
LPR ≥1 time per day	9 (33)
HER ≥5 times per day	17 (63)

Abbreviations: AOA, adult-onset asthma; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DMS, DeMeester score; GERD, gastroesophageal reflux disease; HER, high esophageal reflux; IAL, intra-abdominal lower esophageal sphincter length; LA, Los Angeles; LES, lower esophageal sphincter; LESL, total lower esophageal sphincter length; LESP, lower esophageal sphincter pressure; LPR, laryngopharyngeal reflux; PPI, proton pump inhibitors.

[a] Percentages do not add to 100 because patients may have both types of symptoms.

[b] One patient had an invalid manometry result.

Table 2. Pattern of Proximal Exposure in Patients With AOA

Stratification of Events by Group	Pattern of Exposure in Patients With AOA											
	LPR Events (n = 28)						High Esophageal Reflux Events (n = 242)					
	Position		pH		Composition		Position		pH		Composition	
	Upright	Supine	Acid	Nonacid	Liquid	Mix	Upright	Supine	Acid	Nonacid	Liquid	Mix
Abnormal proximal exposure (+), No.	25	3	23	5	19	9	221	9	148	82	111	119
Abnormal proximal exposure (−), No.	0	0	0	0	0	0	12	0	7	5	10	2
All patients with AOA, No. (%)	**25** (89.3)	**3** (10.7)	**23** (82.1)	**5** (17.9)	**19** (67.9)	**9** (32.1)	**233** (96.3)	**9** (3.7)	**155** (64.0)	**87** (36.0)	**121** (50.0)	**121** (50.0)

Abbreviations: AOA, adult-onset asthma; LPR, laryngopharyngeal reflux.

ferent between those with and without abnormal proximal exposure. The prevalence of hiatal hernia was comparable between groups; however, a type III paraesophageal hernia was found in 2 patients without abnormal proximal exposure. Nearly half of patients in both groups had esophageal mucosal injury; however, patients with abnormal proximal exposure were more likely to have more severe forms of esophagitis, such as Los Angeles classification grade C. Approximately 40% of patients with abnormal proximal exposure had abnormal esophageal motility, whereas most patients without abnormal proximal exposure had normal esophageal motility. Patients with abnormal proximal exposure more often had a defective LES in both the supine and upright positions, indicating more pronounced valve incompetency compared with those without abnormal proximal exposure.

OUTCOMES OF ARS AND COMPARISON WITH PATIENTS WITH A POSITIVE vs NEGATIVE DEMEESTER SCORE

Of 19 patients with abnormal proximal exposure, 18 subsequently underwent ARS, including Nissen (n = 15) or Dor (n = 2) fundoplication and Roux-en-Y esophagojejunostomy (n = 1) (**Table 4**). Roux-en-Y esophagojejunostomy was performed in 1 patient who previously underwent fundoplication for GERD. Of 8 patients without abnormal proximal exposure, 2 underwent repair of a type III paraesophageal hernia with Nissen fundoplication.

Of the 20 patients who underwent ARS, 18 (90%) had either complete resolution (n = 2) or significant improvement (n = 16) of asthma symptoms, 6 of whom had reduced or discontinued pulmonary medications such as corticosteroids (n = 3), bronchodilators (n = 2), or allergy medications (n = 3) at a mean (range) follow-up period of 4.6 (0.6-15.2) months. All patients who underwent ARS were able to discontinue antisecretory medications, such as PPI and H2 antagonists. There was no significant difference in symptomatic response and reduction or discontinuation of asthmatic medications between patients with positive and negative DeMeester scores. There was a trend toward longer duration of esophageal acid exposure in patients with a positive DeMeester score, and esophageal mucosal injury was more often found in patients with a positive DeMeester score (86% vs 18%; $P = .009$).

Asthma symptoms did not change after ARS in 1 patient and improved for only 2 months and then recurred in another patient. The patient with no symptomatic improvement had a significant coughing paroxysm at 2 weeks after the initial ARS and typical GERD symptoms recurred. Subsequent pH testing revealed a DeMeester score of 21. Subsequently, a second ARS was performed and a partially disrupted fundoplication was repaired. No follow-up data were available for the patient with recurrent symptoms at 2 months after ARS.

Pulmonary function test results before and after ARS were available in 5 patients with preoperative abnormal proximal exposure, of whom the forced expiratory volume in the first second of expiration and the peak expiratory flow rate improved in 4 and 3 patients, respectively, at a mean (range) follow-up of 7.3 (0.7-15.2) months after ARS (**Figure 3**). All these patients had symptomatic resolution or improvement. Both the forced expiratory volume in the first second of expiration and the peak expiratory flow rate decreased after ARS in 1 patient who did not have symptomatic improvement.

COMMENT

Some patients with asthma are refractory to medical therapy, and GERD has been suggested as a potential cause or cofactor under these circumstances. In the present study, concomitant typical GERD symptoms and objective findings of GERD were commonly observed in patients with AOA; however, only 30% of patients had a positive DeMeester score. This finding suggests that patients with AOA often have GERD but only a small fraction would be detected with conventional pH testing, which has served as the criterion standard in establishing the diagnosis. To compound the lack of testing sen-

Table 3. Asthmatic Patients With and Without Abnormal Proximal Exposure

Variable	Patients: With Abnormal Proximal Exposure (n = 19)	Patients: Without Abnormal Proximal Exposure (n = 8)	*P* Value[a]
Age, mean (range)	52 (23-73)	57 (48-74)	.41
Sex, No.			
Male	2	2	.33
Female	17	6	
BMI, mean (range)	30.4 (21.9-42.5)	28.2 (21.0-40.3)	.22
GERD symptoms, No. (%)			
Typical	14 (74)	5 (63)	.66
Atypical	6 (32)	4 (50)	.37
PPI dependence, No. (%)	15 (79)	6 (75)	.82
HMII-asthma symptom correlation			
Median (IQR)	8.0 (0-21.5)	0 (0-9.25)	.48
Range	(0-38)	(0-67)	
Mean acid clearance time, s			
Median (IQR)	111.0 (51.0-189.5)	85.0 (45.5-165.0)	.73
Range	(0-445)	(0-488)	
Total acid exposure time per day, min			
Median (IQR)	36.4 (14.9-90.1)	9.1 (2.4-14.4)	.045
Range	(0-308.9)	(0-93.8)	
Hiatal hernia, No. (%)	11 (58)	4 (50, including 2 PEH)	.60
Esophageal mucosal injury, No. (%)	8/17 (47)	3/6 (50)	
Esophagitis, LA classification, No.			
A	2	2	
B	1	1	
C	3	0	
D	0	0	
Barrett esophagus, No.	3	0	
Esophageal motility disorder, No.			
Normal	11	7	.18
Abnormal	7	1	
Defective LES, No. (%)			
Supine	7/14 (50)	3/6 (50)	
Upright	8/14 (57)	5/6 (83)	
Composition of proximal reflux events, %			
Liquid	50.4	83.3	
Mixed	49.6	16.7	
Total reflux events, mean (range)	31.2 (10.0-61.0)	6.9 (2.0-14.0)	<.001
DMS, mean (range)	15.8 (0.8-89.7)	4.6 (0.8-21.0)	.04
Positive DMS, No. (%)	7 (37)	1 (13)	.21
Abnormal proximal exposure			
LPR event			
Median (IQR)	0 (0-2)	0 (0-0)	.02
Range	(0-7)	(0-0)	
HER event			
Median (IQR)	12 (9-15)	1.5 (0.75-2.25)	<.001
Range	(4-20)	(0-3)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DMS, DeMeester score; GERD, gastroesophageal reflux disease; HER, high esophageal reflux; HMII, hypopharyngeal multichannel intraluminal impedance; IQR; interquartile range; LA, Los Angeles; LES, lower esophageal sphincter; LPR, laryngopharyngeal reflux; PEH, paraesophageal hernia; PPI, proton pump inhibitors.

[a] $P < .05$ is considered significant.

sitivity, single-position distal esophageal pH testing does not yield useful information regarding the proximity of reflux events. Therefore, patients with a negative DeMeester score but positive abnormal proximal exposure would be missed using the current diagnostic strategy. Finally, in the setting of AOA, there were very few clinical factors that differentiated patients with abnormal proximal exposure from those without abnormal proximal exposure. For example, in this study there was no difference in symptoms, body mass index, prevalence of hiatal hernia, or age between those with and without abnormal proximal exposure. Because of our inability to clinically stratify patients with AOA with abnormal proximal exposure, there is a tremendous need for an objective measure, such as HMII.

Abnormal proximal exposure as defined by HMII was prevalent in patients with AOA despite a frequently negative DeMeester score, and ARS positively affected not only symptomatic improvement but also a reduction of asthma medications and improvement in pulmonary function in patients with abnormal proximal exposure. These findings suggest that abnormal proximal exposure can cause

Table 4. Outcomes of Surgery and Comparison of 20 Patients With Positive and Negative DeMeester Scores

Outcome of ARS	Patients		*P* Value[a]
	With Positive DMS (n = 7)	With Negative DMS (n = 13)	
(+) Symptomatic improvement or resolution, No. (%)	6 (86)	12 (92)	.64
(−) Symptomatic improvement, No. (%)	1 (14)[b]	1 (8)[c]	.64
Reduction or discontinuation of asthmatic medications, No. (%)	2 (29)	4 (31)	.92
Abnormal proximal exposure, No. (%)	7/7 (100)	11/13 (85)	.27
Mean acid clearance time, s			
Median (IQR)	139 (51-290)	110 (39-144)	.54
Range	(17-445)	(0-488)	
Total acid exposure time per day, min			
Median (IQR)	6.0 (4.2-9.3)	0 (0-14.7)	.28
Range	(0-96.4)	(0-26.2)	
Improvement in PEF or FEV_1	0/1	4/4	.03
Esophageal mucosal injury, No. (%)	6/7 (86)	2/11 (18)	.009
DeMeester score, mean (range)	33.8 (17.1-89.7)	5.0 (0.8-11.5)	<.001
Type of ARS, No.			
Nissen	17		
Dor	2		
Roux-en-Y	1		
Follow-up period after ARS, mean (range), mo	4.6 (0.6-15.2)		

Abbreviations: ARS, antireflux surgery; DMS, DeMeester score; FEV_1, forced expiration volume in the first second of expiration; IQR, interquartile range; PEF, peak expiratory flow.

[a] $P < .05$ is considered significant.

[b] Nissen; failed fundoplication.

[c] Roux-en-Y; no symptomatic change.

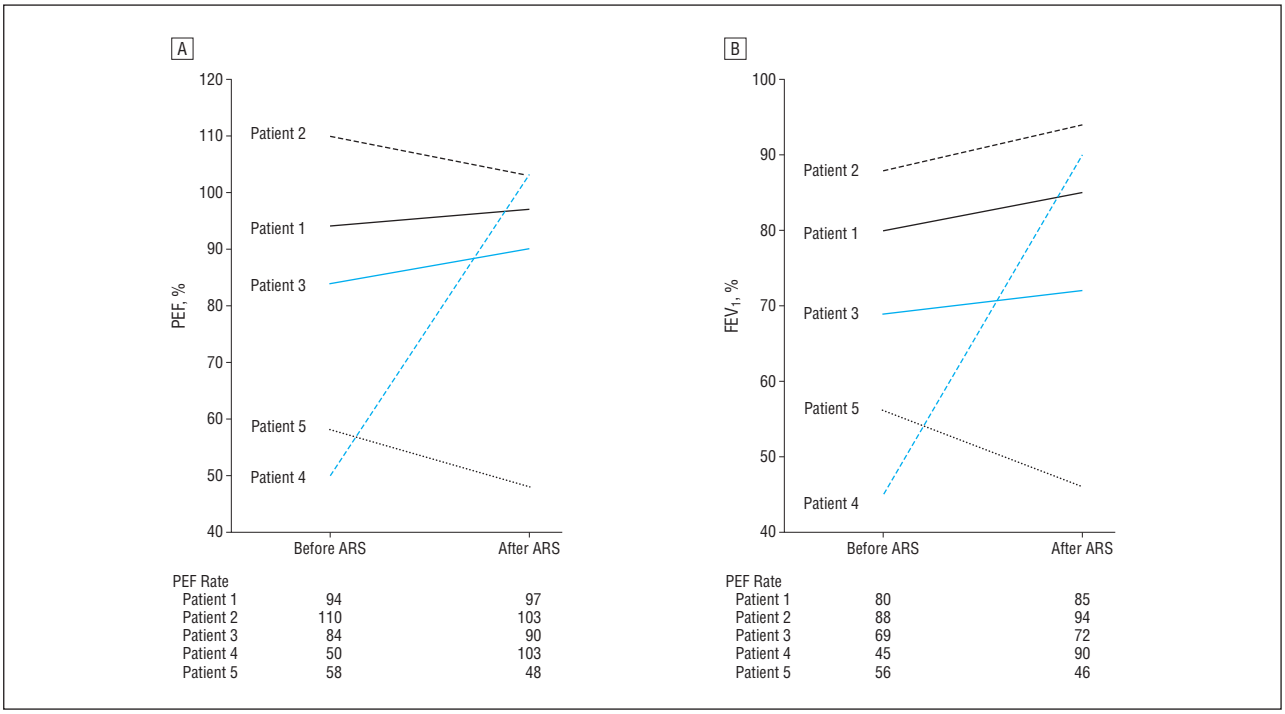

Figure 3. Pulmonary function testing before and after antireflux surgery (ARS). Of the 5 patients who underwent pulmonary function testing after ARS, 3 demonstrated improvement of the peak expiratory flow (PEF) rate (A), and 4 showed improvement in forced expiratory volume in the first second of expiration (FEV_1) (B). All these patients (except the one with decreasing lung function) had symptomatic relief after ARS.

asthma, and HMII successfully identified a subgroup of patients with AOA who will likely respond to ARS. Although the number of patients who underwent ARS in this study is small and the follow-up is short term, the initial results suggest that HMII provides an improvement in the sensitivity of diagnosis of GERD-related AOA (compared with pH testing) and can be used to guide clinical decision making. In addition, because of the poor correlation between abnormal proximal reflux and asthma symptoms, it is unlikely that pH testing combined with

a symptom index would be of any benefit in the patient with AOA (**Table 5**).

Numerous clinical trials[13-17] have demonstrated the variable effectiveness of antisecretory therapy using PPI and/or H2 blockade in patients with poorly controlled asthma. Two randomized controlled studies[18,19] have shown that there was minimal improvement in pulmonary function or asthma symptoms using PPI, and a meta-analysis[26] concluded that there is insufficient evidence to recommend the use of PPI as part of the routine treatment for asthma. Proton pump inhibitors can reduce the acidity of gastric contents but do not address the impaired barrier function of the LES. Therefore, it is reasonable to suggest that PPI do not improve asthma caused by direct laryngopharyngeal exposure, and ARS could be used to recreate the anatomic barrier to all forms of reflux (acid and nonacid), thereby providing a tangible clinical benefit. Several studies have reported that ARS improves asthma symptoms in 49% to 84% of patients with asthma and GERD.[27-31] However, the outcomes of ARS have been inconsistent and have not always positively influenced pulmonary function or pulmonary medication requirements. The enrollment criteria for the previous studies that used ARS in the setting of AOA were heterogeneous and based on factors such as clinical symptoms, endoscopic findings of esophageal mucosal injury, or positive pH testing without direct measurement of laryngopharyngeal and high esophageal reflux events, and this lack of diagnostic sensitivity may have negatively affected the results of this intervention.

Recently, bipositional high resolution manometry was demonstrated to be useful in determining the severity of impaired LES function, especially in patients with isolated upright reflux, in whom a defective LES was found only in the upright position.[32] In the present study, half of patients with abnormal proximal exposure had a defective LES regardless of body position, suggesting that they had a more severe form of GERD and a completely defective LES. Moreover, the pharyngeal reflux events in patients with AOA were more likely to be acid and liquid, and this finding is also consistent with the data in a previous study,[32] in which poor LES integrity led to pure liquid pharyngeal reflux (instead of mixed liquid and gas) through a gastroesophageal valve with a large diameter and high compliance. This is further supported by the fact that patients with abnormal proximal exposure likely have prolonged acid exposure time, more severe forms of esophageal mucosal injury, and abnormal esophageal motility compared with those without.

In the present study, there are some limitations. Objective symptom assessment using a validated questionnaire, such as the GERD health-related quality of life score, was not performed to evaluate the outcomes of ARS. However, all patients were thoroughly interviewed at every follow-up visit and their responses accurately recorded. In addition, most patients had not undergone pulmonary function testing after ARS; thus, it remained unclear whether ARS positively influences pulmonary function in all patients. The sample size (n = 27) may be small, potentially leading to a type II error. The follow-up period may be too short to understand the durability of the benefit of ARS observed in this study. Finally, the specificity of HMII in the context of AOA is unknown; it is possible that there were false-negative interpretations in this investigation, which could represent a limitation of HMII. To validate our proposed criteria and indications for ARS, a prospective, randomized controlled study with a long-term follow-up is required.

Table 5. Proposed Indication for ARS in Patients With AOA

Proposed Indication
Patients with AOA refractory to standard asthma medications (consider HMII)
(+) Abnormal proximal exposure:
LPR event ≥1 time per day and/or HER event ≥5 times per day based on HMII
Regardless of whether there is a positive DMS or objective findings of mucosal injury

Abbreviations: AOA, adult-onset asthma; ARS, antireflux surgery; DMS, DeMeester score; HER, high esophageal reflux; HMII, pharyngeal multichannel intraluminal impedance; LPR, laryngopharyngeal reflux.

In conclusion, AOA may be associated with abnormal proximal exposure as measured by HMII, which likely responds to ARS regardless of whether there is a positive DeMeester score or endoscopic findings of esophageal mucosal injury. Patients with AOA should undergo objective esophageal testing, including HMII, to evaluate for GERD and the proximity of reflux events.

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REFERENCES

1. Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. *JAMA*. 2002;287(15):1972-1981.
2. Kiljander TO, Laitinen JO. The prevalence of gastroesophageal reflux disease in adult asthmatics. *Chest*. 2004;126(5):1490-1494.
3. Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med*. 2000; 162(1):34-39.
4. Amarasiri LD, Pathmeswaran A, de Silva HJ, Ranasinha CD. Prevalence of gastro-oesophageal reflux disease symptoms and reflux-associated respiratory symptoms in asthma. *BMC Pulm Med*. 2010;10:49. doi:10.1186/1471-2466-10-49.
5. Field SK, Underwood M, Brant R, Cowie RL. Prevalence of gastroesophageal reflux symptoms in asthma. *Chest*. 1996;109(2):316-322.
6. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma: summary report 2007. *J Allergy Clin Immunol*. 2007;120(5)(suppl):S94-S138.
7. Kollarik M, Ru F, Undem BJ. Acid-sensitive vagal sensory pathways and cough. *Pulm Pharmacol Ther*. 2007;20(4):402-411.

8. Ishikawa T, Sekizawa SI, Sant'Ambrogio FB, Sant'Ambrogio G. Larynx vs esophagus as reflexogenic sites for acid-induced bronchoconstriction in dogs. *J Appl Physiol*. 1999;86(4):1226-1230.
9. Canning BJ, Mori N, Mazzone SB. Vagal afferent nerves regulating the cough reflex. *Respir Physiol Neurobiol*. 2006;152(3):223-242.
10. Adhami T, Goldblum JR, Richter JE, Vaezi MF. The role of gastric and duodenal agents in laryngeal injury: an experimental canine model. *Am J Gastroenterol*. 2004;99(11):2098-2106.
11. Field SK, Evans JA, Price LM. The effects of acid perfusion of the esophagus on ventilation and respiratory sensation. *Am J Respir Crit Care Med*. 1998;157 (4, pt 1):1058-1062.
12. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med*. 1994;149(1): 160-167.
13. Harding SM, Richter JE, Guzzo MR, Schan CA, Alexander RW, Bradley LA. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med*. 1996;100(4):395-405.
14. Ford GA, Oliver PS, Prior JS, Butland RJ, Wilkinson SP. Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-oesophageal reflux: a placebo-controlled cross-over study. *Postgrad Med J*. 1994;70(823):350-354.
15. Teichtahl H, Kronborg IJ, Yeomans ND, Robinson P. Adult asthma and gastro-oesophageal reflux: the effects of omeprazole therapy on asthma. *Aust N Z J Med*. 1996;26(5):671-676.
16. Meier JH, McNally PR, Punja M, et al. Does omeprazole (Prilosec) improve respiratory function in asthmatics with gastroesophageal reflux? a double-blind, placebo-controlled crossover study. *Dig Dis Sci*. 1994;39(10):2127-2133.
17. Levin TR, Sperling RM, McQuaid KR. Omeprazole improves peak expiratory flow rate and quality of life in asthmatics with gastroesophageal reflux. *Am J Gastroenterol*. 1998;93(7):1060-1063.
18. Boeree MJ, Peters FT, Postma DS, Kleibeuker JH. No effects of high-dose omeprazole in patients with severe airway hyperresponsiveness and (a) symptomatic gastro-oesophageal reflux. *Eur Respir J*. 1998;11(5):1070-1074.
19. Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Gastroesophageal reflux in asthmatics: a double-blind, placebo-controlled crossover study with omeprazole. *Chest*. 1999;116(5):1257-1264.
20. Mastronarde JG, Anthonisen NR, Castro M, et al; American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med*. 2009;360(15):1487-1499.
21. Asano K, Suzuki H. Silent acid reflux and asthma control. *N Engl J Med*. 2009;360 (15):1551-1553.
22. Hoppo T, Sanz AF, Nason KS, et al. How much pharyngeal exposure is "normal"? normative data for laryngopharyngeal reflux events using hypopharyngeal multichannel intraluminal impedance (HMII). *J Gastrointest Surg*. 2012; 16(1):16-25.
23. DiBaise JK. The LA classification for esophagitis: a call for standardization. *Am J Gastroenterol*. 1999;94(12):3403-3404.
24. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. *Am J Physiol Gastrointest Liver Physiol*. 2006;290 (5):G1033-G1040.
25. Johnson LF, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus: a quantitative measure of gastroesophageal reflux. *Am J Gastroenterol*. 1974; 62(4):325-332.
26. Chan WW, Chiou E, Obstein KL, Tignor AS, Whitlock TL. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med*. 2011;171(7):620-629.
27. Rakita S, Villadolid D, Thomas A, et al. Laparoscopic Nissen fundoplication offers high patient satisfaction with relief of extraesophageal symptoms of gastroesophageal reflux disease. *Am Surg*. 2006;72(3):207-212.
28. Sontag SJ, O'Connell S, Khandelwal S, et al. Asthmatics with gastroesophageal reflux: long-term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol*. 2003;98(5):987-999.
29. Patti MG, Arcerito M, Tamburini A, et al. Effect of laparoscopic fundoplication on gastroesophageal reflux disease–induced respiratory symptoms. *J Gastrointest Surg*. 2000;4(2):143-149.
30. Kaufman JA, Houghland JE, Quiroga E, Cahill M, Pellegrini CA, Oelschlager BK. Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease (GERD)–related airway disorder. *Surg Endosc*. 2006;20(12):1824-1830.
31. Iqbal M, Batch AJ, Moorthy K, Cooper BT, Spychal RT. Outcome of surgical fundoplication for extraoesophageal symptoms of reflux. *Surg Endosc*. 2009;23 (3):557-561.
32. Hoppo T, Komatsu Y, Nieponice A, Schrenker J, Jobe BA. Toward an improved understanding of isolated upright reflux: positional effects on the lower esophageal sphincter in patients with symptoms of gastroesophageal reflux. *World J Surg*. 2012;36(7):1623-1631.