CHEST

The Prevalence of Gastroesophageal Reflux in Patients With Excessive Central Airway Collapse

Adnan Majid, MD, FCCP; Fayez Kheir, MD; Daniel Alape, MD; Michael Kent, MD; Anthony Lembo, MD; Vikram V. Rangan, MD; Megan Carreiro, MSc; and Sidhu P. Gangadharan, MD

BACKGROUND: Gastroesophageal reflux (GER) is increasingly recognized as an exacerbating or causal factor in several respiratory diseases. There is a high prevalence of GER in infants with airway malacia. However, such data are lacking in adults.

METHODS: This retrospective study was conducted to determine the relationship between GER and excessive central airway collapse (ECAC). The study included consecutive patients with ECAC referred to the Complex Airway Center at Beth Israel Deaconess Medical Center who underwent esophageal pH testing for GER between July 2014 and June 2018.

RESULTS: Sixty-three of 139 patients with ECAC (45.3%) had documented GER as shown by an abnormal esophageal pH test result. The mean DeMeester score was 32.2, with a symptom association probability of 39.7% of GER-positive patients. Twenty-nine of 63 patients (46%) with GER reported improvement in respiratory symptoms following maximal medical therapy or antireflux surgery without requiring further treatment for ECAC.

CONCLUSIONS: GER is prevalent among patients with ECAC, and aggressive reflux treatment should be considered in these patients prior to considering invasive airway procedures or surgery.

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KEY WORDS: excessive central airway collapse; excessive dynamic airway collapse; gastroesophageal reflux; tracheobronchomalacia

ABBREVIATIONS: DMS = DeMeester score; ECAC = excessive central airway collapse; EDAC = excessive dynamic airway collapse; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; SAP = symptom association probability; TBM = tracheobronchomalacia

AFFILIATIONS: From the Division of Thoracic Surgery and Interventional Pulmonology (Drs Majid, Kheir, Alape, Kent and Gangadharan; and Ms Carreiro), and the Division of Gastroenterology (Drs Lembo and Rangan,), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Drs Majid and Kheir contributed equally to the preparation of the manuscript.

CORRESPONDENCE TO: Adnan Majid, MD, FCCP, Section of Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Rd, Deaconess-201, Boston, MA 02215; e-mail: amajid@bidmc.harvard.edu

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Tracheobronchomalacia (TBM) and excessive dynamic airway collapse (EDAC) are increasingly recognized conditions that affect the trachea, leading to symptoms of airway obstruction.[1-3] TBM is characterized by weakening of the tracheal/bronchial cartilage, which results in an airway that is much more collapsible than normal. EDAC is defined as excessive forward displacement of the membranous wall due to atrophy of the muscular fibers in the posterior membrane of the airway without cartilage collapse.[1-4] Excessive central airway collapse (ECAC) includes both EDAC and TBM. ECAC commonly occurs in patients with chronic airway inflammation.[5] Approximately 23.3% of patients with chronic bronchitis, 14.1% of patients with chronic cough, and 12.7% with known lung disease had evidence of ECAC while undergoing bronchoscopy.[6-8] Gastroesophageal reflux disease (GERD) is a common disease occurring in approximately 18% to 28% of the US population.[9] In addition to its negative impact on patients' quality of life and productivity,[10] GERD is a risk factor for the development of Barrett's esophagus and adenocarcinoma.[11] GER has been associated with a number of pulmonary diseases, including interstitial lung disease, COPD, and asthma, as well as among infants with airway malacia.[11-16] In infants with airway malacia, one of the possible mechanisms is from gastric content aspiration due to gastroesophageal reflux (GER), which may disrupt the mucous membrane of the trachea surface, thereby causing an inflammatory reaction in the airways and lungs.[16] However, the association and prevalence of GER in the adult population with ECAC are less clear. Previous studies from our group have shown a prevalence of 28% to 48% in patients with ECAC; nonetheless, this number has been based on self-reported symptoms and not a formal pH esophageal study.[17,18] The purpose of the present study was to determine the prevalence of GER among adult patients with ECAC.

Patients and Methods

We prospectively collected data between July 2014 and June 2018 of all patients with ECAC referred to the Complex Airway Center at the Beth Israel Deaconess Medical Center. The study protocol was approved by the Beth Israel Deaconess Medical Center institutional review board (institutional review board no. 2014-P-000013) with a waiver of informed consent.

Subject Population

A cohort of 189 consecutive patients with symptomatic ECAC was investigated; 139 had a formal GER evaluation. The diagnosis of severe symptomatic ECAC was based on objective data: dynamic flexible bronchoscopy (decrease in anteroposterior distance) and/or dynamic CT scan (decrease in cross-sectional area) of > 90% collapse along with clinical symptoms (cough, dyspnea, and/or recurrent infections).

Esophageal pH Testing

Patients underwent esophageal reflux testing with either a 24-h impedance-pH or a 48-h esophageal Bravo pH test (Medtronic). Prior to testing, antireflux medication was discontinued (proton pump inhibitors for 7 days, anti-H_2-blockers for 72 h, and antacids (eg, Mylanta [McNeil Consumer Pharmaceuticals Company]) for 24 h prior to testing). The results of reflux studies were interpreted by an experienced gastroenterologist (A. L.). Patients were instructed to keep a diary of meals, periods of sleep, and symptoms of reflux. In addition to total percent time pH was < 4.0, the symptom association probability (SAP) and the DeMeester score (DMS) were evaluated.

Symptom Association Probability: SAP is a method created by Bredenoord et al[19] that expresses the association between a patient's symptoms (eg, regurgitation, cough, heartburn) and episodes of reflux. SAP is calculated by dividing the 24-h pH segments into consecutive 2-min segments. Each segment is evaluated for the presence of symptoms and association with reflux. By statistical convention, SAP > 95% is positive.

Symptoms Index: The symptoms index was created to address the relationship between GER and symptoms. It is defined as the number of times the symptoms occurred while pH is < 4.0, divided by the total number of times the symptoms were recorded, multiplied by 100%: symptoms index = (number of symptoms with pH < 4/total number of symptoms) × 100%. Values > 50% are considered positive for correlation.[20]

DeMeester Score: The DMS is an international standardized score that assesses the global exposure of esophageal reflux. This score is calculated based on six different components: percent total time pH < 4, percent upright time pH < 4, percent supine time pH < 4, number of episodes, number of episodes > 5 min, and longest episode. DMS > 14.7 is considered positive.[21]

Bravo Esophageal pH Probe Testing: A catheter-free Bravo esophageal pH system was placed under endoscopic guidance 6 cm proximal to the gastroesophageal junction per a standard protocol. The wireless esophageal pH-monitoring capsule was placed under endoscopic guidance. Data were interpreted for each 24-h period, and the 24-h period with the highest DMS was used.

Ambulatory 24-h Combined Impedance-pH Testing: Impedance-pH testing was performed by using the Sleuth (Sandhill Scientific) recording system. The impedance-pH catheter was placed into the distal esophagus such that the pH sensor was located 5 cm proximal to the manometrically measured lower esophageal sphincter while the pharyngeal pH sensor was placed 0.5 to 1.0 cm below the proximal upper esophageal sphincter, and left in place for 24 h.

Statistical Analysis

Statistical analysis was performed by using SPSS version 21.0 for Macintosh (IBM SPSS Statistics, IBM Corporation), with a P value < .05 defined as significant. Quantitative variables were expressed as mean ± SD, and categorical variables as absolute and relative frequencies. Student t tests were used for continuous variables, and the Fisher exact test was used for categorical variables.

ECAC Evaluation

I-Dynamic Bronchoscopy Protocol: Patients with suspected ECAC underwent bronchoscopy per our standard protocol[22] under minimal sedation using IV midazolam and fentanyl to allow spontaneous respiration along with lidocaine. The bronchoscope was introduced into the proximal trachea at the level of the cricoid. At that point, patients were instructed to take a deep breath, hold it, and then blow it out (forced expiratory maneuver). Maneuvers were performed at the following six sites: proximal trachea at the level of the cricoid; mid-trachea 5 cm proximal to the carina; distal trachea 2 cm proximal to the carina; right main stem bronchus at the right tracheobronchial angle; bronchus intermedius; and left main bronchus at the left tracheobronchial angle. The maneuvers were repeated three times to ensure maximal airway narrowing during exhalation. All bronchoscopies were video-recorded and reviewed after the procedure to assess the degree of airway collapse before stent placement. Severe ECAC was defined as a collapse > 90% of the airway during exhalation.

II-CT Central Airway Protocol: All patients were imaged according to our standard low-dose CT central airway protocol,[23] which include imaging during end-inspiratory and continuous dynamic expiratory phases. An experienced thoracic radiologist reviewed the CT images. Using a computerized tracing tool, the inner wall of the airway was hand-traced at the level of maximal collapse in dynamic expiratory images to calculate the cross-sectional area of the airway (in square millimeters). At the same level on end-inspiration images, the cross-sectional area of the airway lumen was determined by using the same method. The percentage of luminal collapse between both respiratory phases was calculated by using the following formula: $[1 - (A_{ee}/A_{ei})]) \times 100$, where A_{ee} is luminal area at end-expiration and A_{ei} is luminal area at end-inspiration. Severe ECAC was diagnosed if the percentage of luminal collapse during dynamic expiration was > 90%.

Results

A total of 139 consecutive patients with symptomatic ECAC and esophageal reflux evaluation were included. The mean age was 58.5 years, with a mean BMI of 34.1 kg/m^2, and 75.5% (105) were women. Of this cohort, 56 patients (40.3%) had heartburn, and 32 patients (23.0%) had regurgitation. Table 1 presents the baseline demographic and clinical characteristics.

A total of 139 patients had formal esophageal pH testing. Of those, 81 underwent 24-h combined impedance-pH study and 58 patients underwent Bravo study.

Sixty-three of 139 patients (45.3%) with ECAC had evidence of pathologic GER. A total of 94 patients had EDAC (48 patients [51.1%] had GER), whereas 45 patients had TBM (15 patients [33.3%] had GER). The mean DMS among all patients testing positive for GER was 32.2 ± 20.6, and the mean DMS among all patients testing negative for GER was 5.1 ± 3.7. Of the 63 patients testing positive for GER, the symptoms index with correlation (≥ 50%) of symptoms with episodes of reflux was positive in 29 patients (46%), and SAP was positive (> 95%) in 25 patients (39.7%) (Table 2). Of those, cough was correlated with pH < 4 in 11 patients, heartburn in nine patients, regurgitation in seven patients, and belch in one patient. In total, 28 patients (20.14%) had hiatal hernia, and eight (5.7%) had esophagitis. Among 81 patients who had a 24-h combined impedance-pH study, 17 (21.0%) had nonacidic reflux (ie, with pH > 4 and < 7) as documented by impedance testing. There was no statistically significant difference in

TABLE 1] Demographic and Clinical Characteristics (N = 139)

Characteristic	GER	No GER	Total	*P* Value
Age, mean ± SD, y	58.8 ± 12.1	58.2 ± 12.6	58.5 ± 12.37	.89
Female sex, No. (%)	50 (79.4)	55 (72.4)	105 (75.5)	.69
BMI, mean ± SD, kg/m^2	35.2 ± 9.1	33.0 ± 9.2	34.0 ± 8.26	.38
Coexisting diseases, No. (%)				
Obesity	43 (68.3)	49 (64.5)	92 (66.2)	.72
Asthma	29 (46.0)	35 (46.1)	64 (46.0)	.94
OSA	19 (30.2)	30 (39.5)	49 (35.2)	.29
COPD	12 (19.0)	6 (7.9)	18 (12.9)	.32
Relapsing polychondritis	2 (3.2)	4 (5.3)	6 (4.3)	.69
GERD symptoms, No. (%)				
Heartburn	33 (52.4)	23 (30.3)	56 (40.3)	.010
Regurgitation	22 (34.9)	10 (13.2)	32 (23.0)	.004

GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease.

TABLE 2] Results According to Reflux Study

Variable	Value
DeMeester score, mean ± SD	
With documented GER	32.2 ± 20.6
Without documented GER	5.1 ± 3.7
Symptoms index, n/N (%)	29/63 (46)
Positive symptom association probability, n/N (%)	25/63 (39.7)
Esophageal pH probe testing, n/N (%)	
With documented GER	29/81 (35.8)
Without documented GER	52/81 (64.2)
Bravo study, n/N (%)	
With documented GER	40/58 (68.6)
Without documented GER	18/58 (31.4)
Impedance testing, n/N (%)	17/81 (21.0)

See Table 1 legend for expansion of abbreviation.

the prevalence of OSA (30.2% vs 39.5%; $P = .29$) or BMI (35.2 vs 33.0 kg/m^2; $P = .38$) in patients with and without GER, respectively.

Sixteen of the 63 patients with ECAC and GER (25.4%) reported subjective improvement of respiratory symptoms of cough and dyspnea following aggressive medical management of GER with high-dose (twice a day) proton pump inhibitors for at least 4 weeks. Reflux Nissen fundoplication surgery was performed in 15 patients (23.8%) and laparoscopic toupet was performed in one patient (2.2%) with diagnosed GER. Among those, 11 patients had failed to improve with medical therapy for GER prior to surgery. Thirteen of 16 patients (81.3%) who underwent surgery reported improvement in respiratory symptoms. Overall, 29 of 63 patients (46%) with GER and ECAC reported subjective improvement of respiratory symptoms with aggressive antireflux treatment (medical therapy and antireflux surgery) without requiring further treatment for ECAC.

EDAC Group

The mean DMS among all patients testing positive for GER was 30.95. Symptoms index with correlation (≥ 50%) of symptoms with episodes of reflux was positive in 20 patients (41.6%), and SAP was positive (>95%) in 16 patients (33.3%). Eleven of 48 patients (22.9%) with EDAC and GER reported subjective improvement in respiratory symptoms of cough and dyspnea following maximal medical management of GER. Eleven of 12 patients (91.7%) who underwent surgery reported improvement in respiratory symptoms.

TBM Group

The mean DMS among all patients testing positive for GER was 36.8. The symptoms index with correlation (≥ 50%) of symptoms with episodes of reflux was positive in nine patients (60%), and SAP was positive (>95%) in nine patients (60%). Five of 15 patients (33.3%) with TBM and GER reported subjective improvement in respiratory symptoms of cough and dyspnea following maximal medical management of GER. Two of four patients (50%) who underwent surgery reported improvement in respiratory symptoms.

Discussion

To the best of our knowledge, this report is the first to describe an association between GER and ECAC in an adult population using comprehensive formal GER evaluation. Severe and symptomatic ECAC can be a very debilitating condition. Patients usually present with symptoms of severe dyspnea, cough, mucostasis, decreased exercise tolerance, or even respiratory failure.[17]

Management of symptomatic ECAC includes supportive treatment of recurrent infections, aggressive therapy for co-existing diseases, pulmonary physiotherapy, CPAP for pneumatic stenting, airway stenting, and in highly selected patients, tracheobronchoplasty.[3,5] Therefore, an understanding and appropriate treatment of contributing medical conditions such as GERD is very important in the successful management of such patients. GERD is becoming increasingly recognized as an exacerbating or causal factor in several respiratory diseases.[24] The prevalence of GER among children with tracheomalacia and laryngomalacia was 70%. Similarly, our study has suggested that a high prevalence of GER exists in adults as well.

The prevalence of GERD in the general population (18%-28%) was defined based on clinical symptoms as at least weekly heartburn and/or acid regurgitation.[9] Although such prevalence was based solely on clinical symptoms without objective data (which may underestimate the overall prevalence), it

seems unlikely that a 17.3% difference between patients with ECAC and the general population is only due to asymptomatic reflux disease.

The main advantage of combined impedance-pH monitoring compared with wireless pH monitoring is the ability to detect nonacidic reflux as well as acidic reflux. It is important to emphasize that nonacidic reflux can cause symptoms that are difficult to distinguish from those caused by acid reflux.[25] In the present study, four patients had nonacidic reflux in the group who underwent combined impedance-pH monitoring.

Furthermore, our study found that approximately 36.4% of patients had OSA and 61.7% were obese (BMI $>$ 30 kg/m^2). The exact mechanism causing the increase in nocturnal GER in patients with OSA remains unclear. During obstructive events, high negative intrathoracic pressures are generated distal to the pharynx, placing patients at increased risk for GER and inhalation of oral material. Although several studies have suggested a temporal association between GER and obstructed airway, this relationship is weak.[26-29] Conversely, obesity has been shown in multiple epidemiologic studies to be associated with GER, and its prevalence increases linearly with BMI.[30-32] The elevated BMI increases intraabdominal pressure, leading to a decreased pressure gradient across the lower esophageal sphincter.[33] However, in this cohort, OSA and/obesity did not affect the prevalence of GER in patients with ECAC, suggesting a possible association between both entities.

Our study found that 46% of patients with GER and ECAC reported subjective improvement of respiratory symptoms with aggressive antireflux treatment without requiring further treatment for ECAC. This finding reflects the importance of evaluating and treating GER in such populations before considering other aggressive surgical interventions such as tracheobronchoplasty.

The present study has several limitations. First, this study found an association between GER and ECAC but not causation. Second, this trial was observational with no controlled arm, and possible potential confounding factors such as obesity or OSA could have contributed to such high prevalence. Although GER might contribute to exacerbations of symptoms or negatively affect patients undergoing tracheobronchoplasty, our study aim was intended to show whether a high GER prevalence exists in patients with ECAC. Future study is needed to show whether aggressive treatment of GER will: (1) prevent progression of ECAC; (2) improve symptoms in such a population; and (3) improve long-term outcomes in patients who undergo tracheobronchoplasty. Furthermore, there was no objective measure of pulmonary improvement after antireflux therapy. Improvement in cough and dyspnea might be unrelated to ECAC in these patients. Patients with significant ECAC considered for more aggressive therapy (stenting or tracheoplasty) usually have an inability to clear secretions (due to the dynamic airway obstruction), a refractory "seal-barking" cough, recurrent pneumonias, and even respiratory failure. This study did not objectively document these symptoms. In addition, no physiologic measures were performed prior to or following GER therapy.

Conclusions

The present study showed that GER is common among an adult population with ECAC. Aggressive lifestyle modification and antireflux therapy should probably be considered for decreasing exacerbations and prior to use of aggressive surgical airway stabilization.

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