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GERD-Related Lung Disease



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Several mechanisms predispose patients with pulmonary disease to gastroesophageal reflux (GERD). Transient lower esophageal sphincter (LES) relaxation may be the result of a vagally mediated reflex that is provoked by lung inflation; alternatively, transient LES relaxation may be the result of increased trans-diaphragmatic pressure from cough and/or wheeze. There also may be mechanical incompetence of the LES secondary to alteration in the chest wall and depression of the diaphragms as seen in patients with obstructive lung disease. In addition, medications used to treat pulmonary disease such as beta-adrenergic agonists, prednisone, and the methylxanthine compounds are associated with decreased LES tone. Pulmonary diseases affected by GERD include GERD-related cough, GERD-triggered asthma, COPD, cystic fibrosis, and interstitial lung disease. GERD may also impact sleep. An empiric trial of lifestyle modification and proton pump inhibitor is successful in identifying patients with GERD-related lung disease. This article will review the identification and management of patients with GERD-associated lung disease.

INTRODUCTION

The esophagus and lung share common embryonic foregut origins and vagal innervation, so it is not surprising that GERD is a potential asthma trig-

ger, a cause of chronic cough, and may have an impact or be a co-morbid condition in many other lung diseases (1). There are two major mechanisms whereby GERD may influence the lung—a vagally mediated reflex, and microaspiration. Both mechanisms are active in both animals models and in humans (2). Lung inflammation, primarily mediated through neuroinflammatory mediators (substance P and tachy-

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kinins), also develops in response to esophageal acid. This article will provide up-to-date information concerning identification and management of patients with GERD-associated lung disease.

GERD-RELATED COUGH

Gastroesophageal reflux is a frequent cause of chronic persistent cough (CPC). There are many causes of CPC. The key to cough resolution is finding the specific underlying cause or causes of the cough and directing therapy toward that cause (3). The three most common causes of CPC are: 1) postnasal drip in 41%–58% of patients, 2) asthma in 24%–59% of patients, and 3) GERD in 41% of patients (4).

Chronic cough has more than one cause in up to 62% of cases and three causes are found in up to 42% of cases, making it important for the clinician to be vigilant and to look for multiple causes.

Approximately 10% of CPC patients have prominent GERD symptoms; however, GERD can be clinically “silent” in up to 75% of patients with GERD-related cough. Clinicians should suspect clinically silent GERD in the non-smoker who is not exposed to irritants and who is not taking ACE inhibitors. A negative methacholine challenge test or lack of improvement on appropriate asthma therapy are other clues that GERD may be participating in CPC. Patients who do not have post-nasal drip, sinusitis, or have failed treatment for these conditions should also be suspect. Other times to consider clinically “silent” GERD as a cause of CPC are when there is no evidence of eosinophilic bronchitis, i.e., eosinophils in the sputum or no response to inhaled or oral corticosteroids (5).

Empiric GERD therapy in selected patients results in cough resolution in 79%. Cough resolution occurs within 8 weeks in 86% of patients, and within 6 weeks in 95% of patients. Surgical fundoplication also improves cough. Examining a mixed population of 287 CPC patients shows that cough was eliminated in 54% and improved in 31% after laparoscopic Nissen fundoplication (6). Potential reasons for cough non-resolution include suboptimal control on GERD therapy and non-acid GERD. Also, the clinician needs to adequately treat co-existing causes of cough that can perpetuate the cough-GERD cycle.

GERD-TRIGGERED ASTHMA

Gastroesophageal reflux is a potential asthma trigger. Asthmatics have a high GERD prevalence and have predisposing factors for GERD development. Therapy of GERD has the potential to improve asthma symptoms.

Heartburn is present in 77% and regurgitation is present in 55% of asthmatics. Furthermore, 41% of asthmatics report respiratory symptoms associated with GERD and 28% of asthmatics actually use their inhalers while experiencing GERD symptoms (7). Similar to chronic cough, GERD may be clinically “silent” in up to 65% of asthmatics who do not have GERD symptoms (8). Other esophageal findings in asthmatics include esophagitis in 43% and abnormal esophageal acid contact times in 82%.

Predisposing factors for GERD development in asthmatics include an increased pressure gradient between the thorax and abdominal cavity that overrides lower esophageal sphincter (LES) pressure. Asthma medications may also predispose to GERD. Theophylline increases gastric acid secretion and lowers LES pressure. Repeated nebulized albuterol inhalations produce a dose-dependent reduction in esophageal motility. Oral corticosteroids for 7 days increase esophageal pH acid contact times in asthmatics without prominent GERD symptoms (3).

Multiple studies show an improvement in asthma symptoms with GERD therapy. In 326 medically treated asthmatics with GERD, medications (primarily H₂-antagonists) improved asthma symptoms in approximately 70% of asthmatics (9). Recently, a double-blind, multicenter, placebo-controlled trial using high-dose proton-pump inhibitor (PPI) therapy for 24 weeks showed that asthmatics on PPI had improvement in quality-of-life variables and had fewer asthma exacerbations compared to those on placebo (10). Surgical fundoplication in asthmatics with GERD results in asthma symptom improvement in 79% of patients.

Predictors of asthma improvement with GERD therapy include asthmatics with difficult-to-control asthma, non-allergic intrinsic asthma, nocturnal asthma, and obesity (body mass index >30 kg/m²). GERD characteristics that predict asthma improvement include the presence of reflux-associated respira-

tory symptoms, regurgitation occurring more than once weekly, and significant esophageal acid on pH testing (11). Future studies may identify asthmatics who are more likely to improve with GERD therapy.

GERD AND OTHER OBSTRUCTIVE LUNG DISEASES

Patients with chronic obstructive pulmonary disease (COPD) have a higher incidence of heartburn and dysphagia and are more likely to use GERD medications than matched controls. Twenty-six percent of respiratory symptoms in patients with COPD and GERD were reported to be associated with GERD symptoms, and GERD symptoms were more prevalent in the patients with a forced expiratory volume in one second less than 50% predicted (12).

GERD is also associated with bronchiectasis, particularly in patients with cystic fibrosis (CF). The prevalence of GERD in CF has been reported as high as 80%–94%, and a correlation between lung function and esophageal function has been demonstrated (13,14). Tracheal acidification during episodes of GER has been demonstrated in CF patients leading to the hypothesis that microaspiration may contribute to the deterioration of lung function or result in exacerbations (13). Furthermore, in a small cohort of patients, fundoplication resulted in a 92% reduction in hospital days for CF exacerbations (15).

GERD AND INTERSTITIAL LUNG DISEASE

In both animal models and humans, pulmonary fibrosis may occur after the aspiration of gastric contents. In a study using 24-hour esophageal pH tests, patients with idiopathic pulmonary fibrosis (IPF) had a greater percentage of total acid contact time and a greater percentage of proximal acid contact time than matched controls. Twenty-five percent of the IPF patients with GERD did not have the “typical” symptoms associated with GERD (16). Patients with IPF are also more likely to have a hiatal hernia than age-matched controls and an association between erosive esophagitis and pulmonary fibrosis has also been demonstrated (17). Although a correlation between GERD and lung function in IPF has not been found, several studies of

scleroderma ILD show an inverse correlation between lung function and GERD (18–20).

GERD AND SLEEP

During sleep, gastric motility and emptying is decreased, and basal gastric acid output is increased in the late evening hours. Sleep also results in marked prolongation in esophageal acid clearance times secondary to suppression of swallowing and cough reflexes, decreased salivary flow, and the suppression of arousal mechanisms. The upper esophageal sphincter pressure is greatly reduced during sleep and nocturnal aspiration of pharyngeal secretions is common.

Seventy-five percent of patients with heartburn complain of sleep disruption, and as a result, the majority of these patients have excessive daytime somnolence. Sleep studies in conjunction with 24-hour esophageal pH tests have shown that GERD results in awakenings and sleep fragmentation. There is also a strong relationship between respiratory symptoms (wheeze, cough) and sleep-related GERD and heartburn. Patients with obstructive sleep apnea have greater number of reflux episodes, greater percentage of acid contact times, and a reduced esophageal clearance compared to controls matched for age, gender, and body mass index. When treated with continuous positive airway pressure, both groups of patients had significant improvement in all parameters (21).

DIAGNOSTIC STRATEGIES FOR GERD-RELATED LUNG DISEASE

Since GERD therapy has the potential to improve respiratory outcomes, identifying patients with GERD-related lung disease is important. All patients should be questioned about GERD symptoms including heartburn and regurgitation. Since GERD may be clinically “silent,” an empiric trial of GERD therapy should be implemented for three months. Empiric GERD therapy includes lifestyle modifications (Table 1) and twice daily PPI therapy. A prokinetic drug can also be considered. Respiratory symptoms and pulmonary function should be monitored over the empiric trial period. If respiratory outcomes improve, then maintenance GERD therapy should be implemented. An empiric trial will

Table 1
Lifestyle therapy for GERD

- Weight loss if obese
- Avoid tight fitting clothes
- Avoid large, high-fat meals
- Avoid eating within 3 hours of bedtime
- Sleep with left side down
- Smoking cessation
- Avoid caffeine, chocolate, peppermint, acidic foods, alcohol, and carbonated drinks

identify asthmatics with GERD-triggered asthma and 80% of subjects with GERD-related cough (1).

If respiratory outcomes do not improve after 3 months of GERD therapy, then esophageal pH testing while on GERD therapy is recommended. If esophageal acid is still present, then escalating medical GERD therapy or referral to a gastroenterologist is indicated. If esophageal acid is controlled, then most likely GERD is not playing a major role in the respiratory disease process, although non-acid reflux cannot be ruled out (22).

Esophageal pH testing can be helpful in patients taking and not taking GERD medications. In GERD-related lung disease, temporal correlation of respiratory events is more important than actual esophageal acid contact times, which may be in the normal range. For instance, cough occurring simultaneously or within 3 minutes of when esophageal pH is <4 predicts cough resolution. In general, esophageal pH testing has a specificity and sensitivity approaching 90% in diagnosing GERD; however, it does not determine whether the patient's respiratory disease is impacted by GERD.

An empiric trial is more cost effective than esophageal pH testing. In an asthma model comparing 11 diagnostic strategies, the most cost-effective approach was starting an empiric trial of omeprazole 20 mg daily for 3 months—reserving esophageal pH testing while on omeprazole for the non-responders (23).

Other diagnostic procedures including esophageal manometry, esophageal impedance monitoring, barium swallow examination, and endoscopy are reserved for respiratory non-responders in whom the clinician strongly suspects GERD-related lung disease, or for

the patient who is considering undergoing surgical fundoplication (24).

MANAGEMENT STRATEGIES FOR GERD-RELATED LUNG DISEASE

Management strategies for patients with GERD-related lung disease include lifestyle modifications (Table 1), medical therapy, and surgical fundoplication. Endoscopic therapies including gastroplasty, radiofrequency energy or injection therapy at the gastroesophageal junction are considered experimental in this population.

Smoking is a predisposing factor for GERD; smoking may result in decreased LES tone and deep inspiration and cough may result in increased transdiaphragmatic pressure (25). In one study, the percentage of time when pH was less than 4.0 was significantly greater while smoking and another demonstrated heartburn episodes to be significantly increased in patients after the resumption of smoking (26,27). Therefore, smoking cessation needs to be emphasized.

Proton pump inhibitors are the mainstay of GERD medical therapy and should be taken approximately 30 minutes before meals. They have an excellent safety profile and many patients have been on long-term PPIs for more than 18 years. After the empiric trial, PPI dosing can be reduced to once daily in most patients. Clinically, there are minimal relevant differences among PPIs and none of them require dosing adjustments for hepatic or renal insufficiency. H_2 -receptor antagonists can be used successfully in some cases. Prokinetic drugs can also be useful in respiratory patients and can be combined with acid-suppressive medications.

Some medications used to treat respiratory diseases may predispose to GERD development including theophylline, repeated doses of inhaled albuterol, and oral corticosteroids. Clinicians should consider the risk-benefit ratio of these medications when prescribing them for GERD patients with respiratory disease.

Surgical fundoplication should be reserved for patients who have a clinical respiratory response with medical GERD therapy except in rare situations. Note that surgery may not replace the need for GERD medications. For instance, in more than 500 patients with chronic cough undergoing laposcopic fundoplication,

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at six months 83% had cough improvement, and at five years this percentage dropped to 71% (24). Surgery also has inherent risks including dysphagia. Fundoplication could be considered in medical GERD therapy non-responders only after extensive, careful, respiratory and esophageal evaluations have been performed preferably at a center that has both esophageal and respiratory expertise. A unique cohort of patients include those in whom persistent symptomatic non-acid reflux has been documented while on PPI therapy. Sometimes fundoplication is used in respiratory patients whose regurgitation is uncontrolled with medical GERD therapy, especially in lung transplant recipients.

Evaluation for pharyngeal muscle dysfunction in patients with recurrent aspiration is also important for selected patients. Chronic GERD therapy should be individualized for each patient. There is no data examining chronic maintenance therapy for GERD-related lung disease.

CONCLUSION

Gastroesophageal reflux can trigger asthma and is a cause of chronic cough, and may impact other respiratory diseases. Careful evaluation, including an empiric PPI trial, is useful in identifying patients with GERD-related respiratory disease. GERD therapy has the potential to improve respiratory outcomes. Both medical and surgical options are available to manage GERD in respiratory patients. ■

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