
Gastroesophageal Reflux as an Asthma Trigger

Acid Stress

Since Sir William Osler recognized that gastro-esophageal reflux (GER) is a potential asthma trigger more than a century ago, multiple investigations have shown a potential interaction between the esophagus and the lung. Despite this, there are still many unanswered questions as to how these two organs interact. To substantiate this interaction and to begin to examine causality, three criteria should be met. First, GER prevalence should be higher in asthmatic patients than in control subjects. Second, GER should alter airway reactivity and inflammatory markers. And third, GER therapy should improve asthma outcomes. So where do we stand concerning acid stress?1,2

GER symptom prevalence is higher in asthmatic patients compared to control subjects. Field et al3 examined 109 asthmatic patients and 135 control subjects in two control groups, finding that heartburn was present in 77% of asthmatic patients compared to 48% of control subjects. Furthermore, 41% of asthmatic patients noted reflux-associated respiratory symptoms, and 28% of them utilized inhalers while experiencing GER symptoms. So, not only do asthmatic patients have a higher prevalence of GER symptoms than control subjects, they also associate GER symptoms with asthma symptoms. Our laboratory noted4 that of 151 respiratory symptoms reported in 199 asthmatic patients during 24-h esophageal pH testing, 79% of respiratory symptoms were temporally related to esophageal acid.

In this issue of CHEST (see page 1490), Kiljander and Laitinen provide further insight into GER prevalence in asthmatic patients. In randomly selected asthmatic patients undergoing 24-h esophageal pH testing, 36% of asthmatic patients had abnormal esophageal acid contact times and 25% of asthmatic patients with abnormal esophageal acid contact times were free of typical GER symptoms including heartburn. Furthermore, heartburn was not always associated with abnormal esophageal acid contact times. So, should esophageal pH testing be performed in asthmatic patients to identify GER in clinical practice? My answer is, no! Although esophageal pH testing is considered to be the “gold standard” for identifying GER, it has a sensitivity and specificity of approximately 90% and is not a perfect test.5 Day-to-day esophageal acid contact times vary with activity and diet. Recently, a wireless esophageal pH system has been developed that allows monitoring up to 48 h without the use of an intranasal catheter, so that patients are less likely to alter their daily activities and/or diet.6 Also, a nonacid refluxate, undetectable with pH monitoring, may have an impact. Currently, minimal data exist on nonacid reflux and its effect on the lung. Nonacid GER can be measured by esophageal impedance monitoring, which was not performed in this study.7 Despite these issues, Drs. Kiljander and Laitinen verify for us again that the prevalence of GER is indeed high in asthmatic patients.

So, why is GER so prevalent in asthmatic patients?2 Predisposing factors include an increased pressure gradient between the thorax and abdomen, leading to more frequent reflux episodes. Asthmatic patients with GER also have a higher prevalence of hiatal hernia (64%) compared to control subjects (19%), predisposing them to GER development.1 Finally, asthma medications may potentiate GER. For instance, theophylline increases gastric acid secretion and decreases lower esophageal sphincter pressure, inhaled β2-adrenergic agonists decrease lower esophageal sphincter pressure in a dose-dependent manner, and oral corticosteroids increase esophageal acid contact times.1,8

If GER is an important asthma trigger, then mechanisms should explain how GER alters airway reactivity and inflammatory markers. The potential mechanisms include a vagally mediated reflex, a local axonal reflex, heightened bronchial reactivity, and microaspiration.1 Furthermore, neurogenic inflammation appears to play a key role in esophageal acid-induced bronchoconstriction. Elegant morphologic studies identified a direct connection between the esophagus and the lung with nitric oxide-containing neurons. In animal models, esophageal afferent nerve stimulation results in action potentials and tachykinin release (substance P and neurokinin-A) in the lung.8 Aspiration may damage the airway epithelium, resulting in the release of cytokines and adhesion molecules leading to neurogenic inflammation and the initiation of other inflammatory pathways.9 These mechanisms are dependent on the activation of capsaicin-sensitive sensory nerves, with the subsequent release of tachykinins that, in conjunction with kinins, nitric oxide, oxygen radicals, and proteases, modulate diverse aspects of airway inflamma-
tion. Thus, excessive acidification leading to “acid stress” has many potential adverse effects on the lung.

So, with this in mind, does antireflux therapy improve asthma outcomes? Previous trials have shown that antireflux therapy improves asthma symptoms in approximately 70% of asthmatic patients with GER. However, these trials had major design flaws, including small patient populations, inadequate asthma outcome analyses, and the use of a placebo crossover design in many of the proton pump inhibitor trials. Another important finding is that pulmonary function improvement does not always follow asthma symptom improvement. The Cochrane Airways Group Registry examined randomized controlled trials of children and adults who had been treated with medical or surgical antireflux therapy, identifying 328 subjects and finding that seven of nine studies had at least one significantly improved asthma outcome. There are hints in large cohort studies that GER may impact asthma. GER was noted to be a risk factor for asthma hospitalization in asthmatic patients over the age of 19. Also, in a retrospective cross-sectional analysis of 10,959 asthmatic patients, GER was predictive for higher numbers of oral steroid bursts and asthma hospitalizations. So GER may be an important asthma trigger in selected asthmatic patients, however, a definitive outcomes study has not been published to date.

A problem with our current state of knowledge is that we do not know which asthmatic patients would benefit from GER therapy. Many asthmatic patients have GER without GER actually being a trigger of their asthma. Potential predictors of asthma response include the presence of regurgitation, nocturnal asthma, nonallergic asthma, difficult-to-control asthma, a history of reflux-associated respiratory symptoms, and a high body mass index. These predictors have not been validated in larger studies, so currently it is up to the clinician to determine whether GER is indeed a trigger of their individual patient’s asthma. A 3-month empiric trial of aggressive acid suppression utilizing a proton pump inhibitor could be used to identify these asthmatic patients. Hopefully, future investigations will allow clinicians to target those asthmatic patients who have acid stress.

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The Oximeter
Boon or Bane?

The patient needed to undergo a closed reduction of a dislocated shoulder in the emergency department where I was training. And, because the patient had been “fall-down drunk” at the time, the