MAYO CLINIC

REVIEW

Aspiration Pneumonia and Related Syndromes

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Abstract

Aspiration is a syndrome with variable respiratory manifestations that span acute, life-threatening illnesses, such as acute respiratory distress syndrome, to chronic, sometimes insidious, respiratory disorders such as aspiration bronchiolitis. Diagnostic testing is limited by the insensitivity of histologic testing, and although gastric biomarkers for aspiration are increasingly available, none have been clinically validated. The leading mechanism for microaspiration is thought to be gastroesophageal reflux disease, largely driven by the increased prevalence of gastroesophageal reflux across a variety of respiratory disorders, including chronic obstructive pulmonary disease, asthma, idiopathic pulmonary fibrosis, and chronic cough. Failure of therapies targeting gastric acidity in clinical trials, in addition to increasing concerns about both the overuse of and adverse events associated with proton pump inhibitors, raise questions about the precise mechanism and causal link between gastroesophageal reflux and respiratory disease. Our review summarizes key aspiration syndromes with a focus on reflux-mediated aspiration and highlights the need for additional mechanistic studies to find more effective therapies for aspiration syndromes.

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Pulmonary aspiration is the pathologic passage of fluid or substances below the level of the vocal cords into the lower airways. Typically, aspiration is considered an acute event that can result in infectious pneumonia, chemical pneumonitis, or even respiratory failure from acute respiratory distress syndrome (ARDS).[1] The pathologic consequence of aspiration has been mostly attributed to the acidity of gastric fluid, but it should be noted that aspiration can occur from multiple sources in addition to the stomach (eg, duodenal, oropharyngeal, exogenous), and the aspirate material may contain other injurious materials (eg, microbes, bile, pepsin, particulates). In this review, we will focus on aspiration syndromes related to gastroesophageal reflux (GER).

In contrast to the more established acute aspiration syndromes, chronic occult pulmonary aspiration, also referred to as *silent aspiration* or *microaspiration*, is considered more often in the outpatient setting and is believed to contribute to the pathophysiology of multiple respiratory disorders, including pulmonary fibrosis, asthma, bronchiectasis, bronchiolitis, chronic bronchitis, pneumonia, chronic cough, and lung transplant rejection (Table 1).[2] Interestingly, these clinical suspicions often go unchallenged with empirical attempts at moderating aspiration, or more typically its prerequisite, GER, by the use of acid suppressants.

The perception that aspiration is an important mechanism and contributor to respiratory disorders is largely due to the apparent increase in the prevalence of gastroesophageal reflux disease (GERD) across both chronic and acute respiratory disorders. However, a well-validated tool to readily diagnose microaspiration is lacking, and many clinicians have adopted the treatment of GERD, typically with a proton pump inhibitor (PPI), into practice in hopes of improving their patient's respiratory condition. Although PPIs do little to directly reduce reflux and are associated with substantial health care costs and potential adverse events, large observational and controlled studies have been increasingly reported in respiratory medicine, more often with negative results. Nonetheless, aspiration remains a dominating concern as the linking mechanism between GERD and chronic respiratory conditions, particularly with fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF), and to a lesser extent in patients with obstructive lung disorders, including asthma and chronic cough.

ARTICLE HIGHLIGHTS

- Reflux is prevalent across a variety of acute and chronic respiratory disorders and is considered a predisposing mechanism for a variety of pulmonary aspiration syndromes.
- Caution should be used when treating suspected pulmonary aspiration syndromes with gastric acid neutralization alone because standard treatment of reflux has not produced clear clinical benefit and may be of potential harm.
- Additional mechanistic studies are needed to understand the causal role of reflux in aspiration and respiratory disorders to identify effective targets of interventions.

MECHANISMS UNDERLYING GER AND ASPIRATION

Mechanistically, it is inadequate and inappropriate to assume that the presence of GER implies that aspiration is occurring. There are multiple factors that may promote reflux and eventual aspiration of gastric fluid into the lower airways but also multiple defenses that must be bypassed before an aspiration event becomes pathologic (Table 2).

First, it is important to clarify what is meant by GERD. Gastroesophageal reflux is the retrograde movement of gastric fluid into the esophagus and notably not a state of excess gastric acidity, which is the target of most GERD therapies. Furthermore, GERD is heterogeneous and multifactorial, with multiple phenotypes identified in advanced esophageal testing and supported by the current Rome IV classification scheme (eg, erosive esophagitis, functional dyspepsia, nonerosive reflux disease, and asymptomatic GERD).[3] Additionally, standardization and advances in high-resolution esophageal manometry have identified differing patterns in esophageal motility among patients with GERD that may be particularly pertinent in patients with respiratory disorders.[4-6] Finally, novel techniques to image the esophagogastric junction (EGJ) directly with fluoroscopic methods and simultaneously measure pressures in the stomach, esophagus, and EGJ and lower esophageal sphincter (LES) with adaptations of the Dent sleeve catheter (Dentsleeve International Ltd) have further facilitated our understanding of how the transdiaphragmatic (ie, gastric to esophageal) pressure gradient (TDPG) interact with the EGJ/LES complex to facilitate reflux. Specifically, because the striated crural muscles of the diaphragm are important to the competence of the EGJ, this provides at least a potential mechanistic link on how the respiratory system may anatomically and physiologically link with GERD.[7] Fundamentally, these 2 factors, the pressure gradient between the stomach and the esophagus (ie, TDPG) and the competency of the EGJ and LES, are what define whether gastric fluid will abnormally enter into the esophagus, including during physiologic transient LES relaxations.[8]

Second, the composition of gastric fluid is an important consideration. In animal models, it is readily recognized that acid is not the sole issue; gastric particulates also augment airway injury.[9,10] Additionally, both pepsin and bile acids promote epithelial damage, not just to the esophageal mucosa but to airway epithelium as well.[11,12] Thus, the constituency and volume of aspirate material are important in the development of respiratory pathology and perhaps help to account for vastly different phenotypic expressions of gastric aspiration (eg, pneumonitis, ARDS, bronchospasm, bronchiolitis, and lung fibrosis).

Next, if gastric contents do reflux into the esophagus, it must traverse the span of the esophagus up into the pharynx (ie, laryngopharyngeal reflux) by bypassing the important barriers of not only the EGJ and LES but also esophageal peristalsis, which act to clear any residual refluxate from the esophagus, further

TABLE 1. Associated Aspiration Syndromes

Acute
Bronchospasm, asthma
Acute bronchitis, COPD exacerbation
Pneumonia, pneumonitis
Foreign body obstruction
Acute respiratory distress syndrome
Chronic
Bronchiectasis, chronic bronchitis
Exogenous lipoid pneumonia
Interstitial lung disease
Organizing pneumonia
Bronchiolitis obliterans syndrome
Diffuse aspiration bronchiolitis

COPD = chronic obstructive pulmonary disease.

TABLE 2. Protective Reflexes to Aspiration and Potential Targets of Therapy

Barriers to aspiration	Potential therapeutic considerations
Laryngopharyngeal	Dietary/behavioral measures
Swallow	Speech therapy (swallow training)
Epiglottis	Increase cough sensitivity (eg, ACE inhibitors)
Vocal cord closure	
Throat clearing, cough	
Esophagus	Dietary/behavioral measures
Upper esophageal sphincter	Agents that reduce TLESRs
Peristalsis (eg, postreflux swallow induced)	Gastric acid neutralization
Lower esophageal sphincter	Promotility agents
Crural diaphragm	EGJ competence (eg, inspiratory muscle training)
Lungs	Increase cough sensitivity
Cough	Bronchial hygiene measures to enhance clearance
Mucociliary barrier	Prociliary agents
Innate immune, inflammatory response	β-Blockers
	Targeted blocking of aberrant inflammatory or fibrotic pathways

ACE = angiotensin-converting enzyme; EGJ = esophagogastric junction; TLESRs = transient lower esophageal sphincter relaxations.

minimizing the possibility that it may reach the upper airways. If the esophageal defenses are breached and proximal refluxate enters the pharynx, there must be both sufficient volume and impairment in the cough or swallow reflexes to allow passage beneath the vocal cords into the lower airways (ie, aspiration). Although diminished consciousness, neurologic disorders, and anatomic changes in the pharynx may impair swallow function, the volume and type of material is also important to whether these protective reflexes are elicited. In normal states, the volume needed to stimulate protective pharyngeal reflexes is typically smaller than the capacity of the hypopharynx wherein aspiration may occur, but this situation can worsen with age or other exogenous factors.[13,14] Additionally, swallow and tussigenic reflexes may not always be triggered by certain substances, particularly oils, which are nearly *aphagetic* (ie, does not elicit a swallow reflex) in cats,[15] and likely explains the often indolent presentation of a classic aspiration syndrome, exogenous lipoid pneumonia.

Even after aspiration has occurred, additional considerations remain, such as cough reflex and mucociliary barrier, mitigating the consequences of aspiration. Indeed, there is evidence to suggest aspiration can occur at physiologic levels without any apparent respiratory consequences. For example, pepsin can be found in saliva and bronchoalveolar fluid (BALF) of normal adults.[16,17] Furthermore, in studies in which radionuclide material is ingested or *dripped* into the pharynx, the material can be detected on scintigraphy within the lungs, particularly during times of depressed consciousness, including physiologic sleep.[18-20] Mucociliary function is an important, although understudied, area for potential targets of intervention to mitigate aspiration-related syndromes, including pneumonias.[21]

Observations that aspiration may occur physiologically and not cause respiratory pathology[22] suggest that other factors are important in whether an aspiration event will lead to respiratory consequences. As noted, although the volume and constituency of the aspirate material is likely important in whether pathology develops, the patient's immunologic response or state may also be critically important in determining whether disease occurs. For example, in animal models of aspiration, a sympathetic surge and consequent depression of the immune system was a modifiable factor (using β-blockers) in the development of both pneumonia and bacteremia following induced aspiration.[23] Thus, the connection between GERD and lung disease by the mechanism of macroaspiration or microaspiration is a complex interplay of proreflux and proaspiration factors, balanced against the barriers that the refluxate must overcome as it traverses

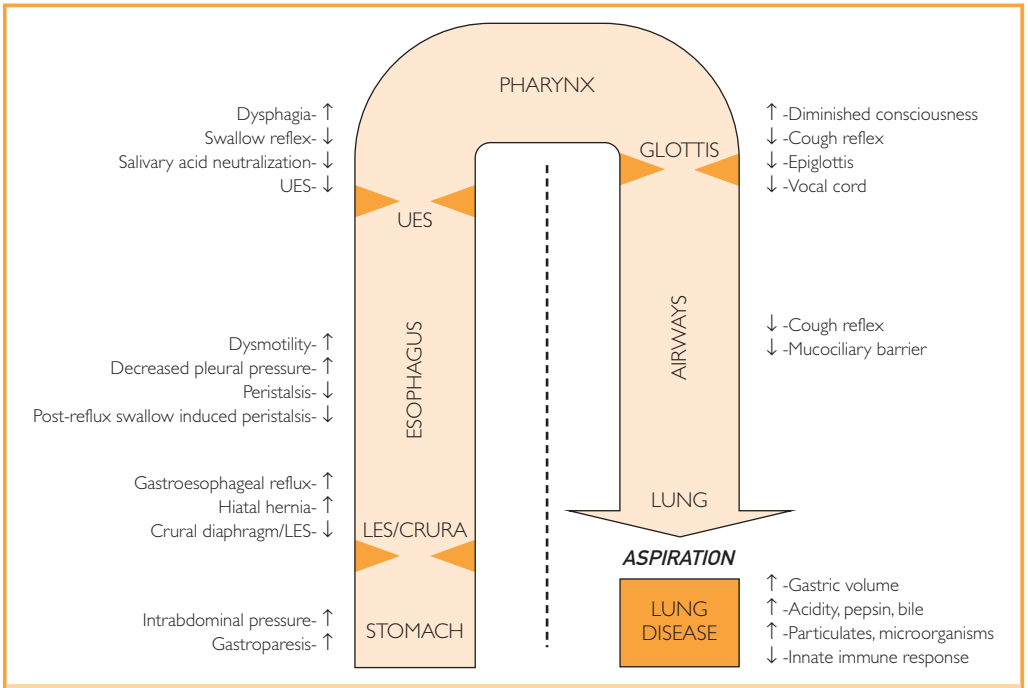

FIGURE. Schematic of the anatomic barriers and protective defenses before gastroesophageal refluxate can reach the lungs and cause disease. LES = lower esophageal sphincter; UES = upper esophageal sphincter; ↓ = factor protective against aspiration; ↑ = factor favoring aspiration and disease.

the esophagus into the airways before it can be pathologic (Figure).

ACUTE ASPIRATION SYNDROMES: PNEUMONIA, ARDS

Acute aspiration syndromes encompass acute respiratory decompensations that may lead to hospitalization. This category includes infectious pneumonia from carriage of oropharyngeal bacteria into the lungs, chemical pneumonitis from gastric juices, and specific clinical syndromes such as ventilator-associated pneumonia and ARDS.

Community-acquired pneumonia is a leading cause of hospitalization and death for which aspiration or inhalation of microbial flora from the oropharynx is the leading pathogenic mechanism.[1,24] The epidemiology of pneumonia suggests a strong correlation with increasing age, and the elderly are particularly susceptible to secondary adverse events such as sepsis, ARDS, and death. Targeting community-acquired pneumonia as an aspiration syndrome (and not just a lower respiratory tract infection) can be clinically effective; a clinical trial randomizing nursing home residents to aggressive oral care or none found professional-assisted oral care led to a decrease in the rate of febrile events, pneumonias, and death from pneumonias.[25] By contrast, multiple observational studies targeting aspiration as a reflux disorder reported that PPIs may increase the risk of community-acquired pneumonia.[25,26] Thus, aspiration can be a target of clinically effective interventions, but a misunderstanding of the aspiration mechanism may lead to adverse outcomes.

Similarly, aspiration is thought to be a common mechanism for hospital-acquired pneumonia, particularly in mechanically ventilated patients. Ventilator-associated pneumonia has been linked to increased morbidity, mortality, and cost.[27] Although treatment strategies historically have been focused on accurate and timely identification of the infectious agents and development of more effective antimicrobials, arguably greater success has been achieved when approaching ventilator-associated pneumonia as a problem of aspiration (eg, bed elevation, subglottic aspiration devices, oral decontamination).[27,28]

Although PPIs can reduce the morbidity and potential mortality of stress ulcers in this setting, they also may increase the risk of hospital-acquired pneumonia.[29]

Some of the original descriptions of ARDS, including by Mendelson[30] and Petty and Ashbaugh,[31] attributed it to aspiration. Although ARDS is now associated with multiple etiologies, aspiration remains the third-leading cause.[1,32] Typically, aspiration in this context is clinically apparent either to the patient or an observer, with overt inhalation of gastric contents following an episode of emesis or regurgitation. However, despite the long-standing recognition of this devastating illness, much of the success in ARDS outcomes has been through strategies to minimize additional injury to the lungs from support devices.[33] By approaching ARDS proactively by its mechanism, such as aspiration, rather than syndromically after it has happened, it may be possible to mitigate progression to respiratory failure and death by early identification and intervention. This is an area of ongoing research, to identify patients at risk for aspiration based on clinical profile[32,34] and specific diagnostic tests that assess phonation, swallow, and cough,[35-37] so that early interventions can be provided (eg, the Checklist for Lung Injury Prevention, oral hygiene, speech therapy, up-regulation of cough reflex) to prevent aspiration.

INTERSTITIAL LUNG DISEASE: IPF, ORGANIZING PNEUMONIA

Outside the acute care setting, there is accumulating evidence for the clinical relevance of microaspiration in chronic respiratory disorders, in particular, fibrotic lung disorders and lung transplant medicine. Microaspiration has been a major concern for IPF, a deadly fibrotic lung disease without a cure. Due to the high prevalence of reflux, up to 94%,[38] and limited treatment options, clinicians have investigated whether microaspiration might be a potential target for IPF therapy. In the most systematic investigation thus far, reflux was not only more common and severe among patients with IPF (compared with other interstitial lung diseases and healthy controls), but a significant correlation was found between lung fibrosis (as scored from high-resolution computed tomography of the chest) and both distal (r^2=0.57) and proximal (r^2=0.63) reflux episodes.[39] In addition to increased proximal reflux episodes, high-resolution esophageal manometry and esophageal pH monitoring reveal that patients with IPF have more hypotonic upper esophageal sphincter when compared with healthy patients (31.8% vs 7.5%), more proximal acid contact reflux times (2.5% vs 0.9%), and longer mean proximal acid clearance times (169.9 seconds vs 42.4 seconds), particularly in the supine position (899.1 seconds vs 47.6 seconds) when patients are thought to be most susceptible to microaspiration.[40]

Although these associations support microaspiration as a linking mechanism between GER and lung fibrosis, definitive evidence of aspiration is not typically seen in pathologic specimens of patients with IPF, which is characterized histologically as usual interstitial pneumonia rather than foreign body granulomatous reactions. As such, investigators have also studied gastric biomarkers in BALF to see if microaspiration can be confirmed. Although the sensitivity of exhaled breath condensate samples to detect pepsin is uncertain, it was able to be measured in 2 of 17 patients with IPF compared with 0 of 6 non-IPF controls (P=.38).[41] In the aforementioned systematic study confirming a correlation between the extent of fibrosis and reflux parameters, pepsin and bile were found in 62% and 67% of bronchoscopic samples from 38 patients with IPF, significantly higher than in patients with non-IPF interstitial lung diseases (25% with pepsin, 25% with bile) and healthy controls (none with pepsin or bile).[39] Furthermore, a significant correlation was again seen between high-resolution computed tomography scores of lung fibrosis with both pepsin (r^2=0.60; P<.01) and bile (r^2=0.46; P<.01), giving credence to the possibility that microaspiration may be involved in the pathogenesis of lung fibrosis.[39]

Of additional clinical importance, microaspiration may account for the often unpredictable and fatal acute exacerbation of IPF. One study found a significantly higher BALF pepsin level in patients with acute exacerbation (P=.04) by bivariate regression analysis.[42] This effect was seen in a third of patients with acute exacerbation of IPF whose pepsin concentrations were in excess of the 95th percentile of stable IPF patients, but notably,

pepsin did not independently predict survival. As a result of accumulating evidence for GER, microaspiration, and IPF, as well as several limited observational studies exploring antireflux therapies,[43-46] clinical trials are under way to determine if antireflux surgery may impact the relentless course of IPF.

Cryptogenic organizing pneumonia is a diagnosis of exclusion, ie, organizing pneumonia of unknown cause with variable clinical and radiographic manifestations. Aspiration as the cause of organizing pneumonia can be missed, even after a surgical lung biopsy. This problem was highlighted in a pathologic series of 59 confirmed cases of aspiration-associated pulmonary diseases (88% manifested organizing pneumonia) in which aspiration was neither suspected clinically (in only 9%) nor identified in the first histologic examination (in only 21%).[47] Thus, aspiration can occur occultly without being evident to patients or clinicians and can be difficult to confirm, even with a surgical specimen. In fact, assuming that many aspiration events are not related to pill or food matter, such foreign body reactions may not be present at all, making the precise role of lung biopsy as the confirmatory procedure for diagnosing aspiration-related lung disease questionable.

POST–LUNG TRANSPLANT CHRONIC ALLOGRAFT DYSFUNCTION

Multiple series have reported the increased prevalence of GER among lung transplant recipients,[48-50] including the importance of nonacid reflux and esophageal dysmotility related to aspiration and development of bronchiolitis obliterans syndrome.[49,51,52] Aspiration in lung transplant recipients has been defined primarily by the detection of pepsin and bile in BALF. The detection of pepsin and bile appears to be prevalent and associated with development of chronic rejection,[53,54] but notably, pepsinogen C can be expressed from type II pneumocytes,[17,55-58] complicating the interpretation of some of these reports. It is likely that the process of transplantation (eg, anatomic distortion, airway denervation, vagal injury, drug effects), rather than the specific respiratory disorder, contributes to the apparent increase in reflux and aspiration.[59]

OBSTRUCTIVE LUNG DISEASES: ASTHMA, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, BRONCHIOLITIS

The evidence for microaspiration in obstructive lung disorders, such as asthma and chronic obstructive pulmonary disease (COPD), is weaker. In chronic asthma, microaspiration data is largely derived from studies utilizing gastric biomarkers in pediatric patients, although not always with data suggesting a correlation with the prerequisite proximal reflux episodes.[60,61] However, most mechanistic studies in adults suggest a neuronal mechanism between reflux and asthma, rather than aspiration. For example, esophageal acid perfusion studies can experimentally worsen airflow (forced expiratory volume in one second, peak expiratory flow rate, or airway resistance) and increase bronchial hyperresponsiveness to methacholine or histamine.[62-66] Moreover, randomized controlled trials using PPI to impact asthma have failed to demonstrate a meaningful benefit,[67,68] although this may be due in part to targeting all asthmatics (and not necessarily those with confirmed reflux-mediated asthma) and targeting exclusively acid reflux rather than all refluxate.[69]

For COPD, acute exacerbations have the highest association with GER,[70-72] which combined with data supporting increased prevalence of swallow dysfunction[73] could suggest that patients with COPD are more likely to aspirate and be the basis for acute exacerbations. However, specific microaspiration data are lacking, with only a single study in which pepsin was detected at a higher level in the sputum of patients with COPD than in controls,[74] and because these are observational studies, some of the differences may have been due to differences in reflux prevalence and severity, smoking status, or common medications used with more advanced or acute exacerbations of COPD (eg, corticosteroids, theophylline, β-agonists, antimuscarinics) that can themselves promote reflux.[75-79]

Diffuse aspiration bronchiolitis is a term used to denote a primarily bronchiolar manifestation of aspiration and generally presents in an insidious and chronic form. Manifestations on computed tomography are characterized by tree-in-bud opacities or micronodules in centrilobular distribution with bronchial wall

thickening.[80] However, confirmation of the diagnosis requires detection of foreign bodies in a biopsy specimen, which may be challenging to identify even with surgical specimens.[47,81] As a result, some are presumptively diagnosed based on clinicoradiographic context, with many, but not all, having a history of recurrent lower respiratory tract infections and risk factors for aspiration, such as reflux, dysphagia, and drug abuse.[82]

Reflux is prevalent in other airway disorders, such as bronchiectasis (the most severe congenital form being cystic fibrosis [CF]), in which microaspiration has been suggested by direct identification of gastric enzymes from airway specimens.[60,74,83] Even though reflux appears predominantly acidic in pediatric patients with CF, a small randomized controlled trial using PPIs found no benefit and suggested a trend toward more exacerbations.[84] This finding highlights again the importance of disconnecting acidic reflux from respiratory disorders when considering microaspiration because neutralization or suppression of gastric acidity will not eliminate reflux events and may promote infectious adverse events in already respiratory-compromised patients.[85] There is also some evidence to support an association between reflux aspiration and non-CF bronchiectasis,[74,86] although it is unclear whether it is a complicating factor, as in CF, or whether aspiration may play an etiologic role.[87]

CHRONIC COUGH

Gastroesophageal reflux is an accepted cause of chronic cough, but it appears that aspiration is an unlikely mechanism. In a cohort of 100 patients with chronic cough, sputum and BALF pepsin levels were measured as indicators of laryngopharyngeal reflux and microaspiration, respectively.[88] They also underwent simultaneous 24-hour ambulatory acoustic cough and multichannel intraluminal impedance and pH monitoring. Not unexpectedly, the number of proximal reflux events (although not distal reflux) correlated modestly with sputum pepsin concentrations (r=0.33; P=.045) but inversely with cough frequency (r=−0.52; P=.04), suggesting that cough may be protective against aspiration, rather than a consequence of aspiration. In support of this theory, pepsin levels in BALF have no correlation with either cough frequency or reflux events.[87] Thus, microaspiration appears unlikely to be a prevalent mechanism for chronic cough, and contrary to conventional wisdom, chronic cough is teleologically a protective reflex against microaspiration.

Similar to asthma, reflux-mediated cough is most likely due to a neuronal esophagobronchial reflex facilitated by a central or peripheral sensitization process rather than aspiration. Both the esophagus and airways are innervated by chemically and mechanically sensitive vagal afferents that converge in the nucleus tractus solitarius, the *cough center*. Findings from a carefully conducted systematic investigation suggested central sensitization as the most important factor in chronic cough by documenting that the only significant predictor of a clear reflux-mediated cough was a lowered cough threshold (as measured by inhaled citric acid tussigenic challenge) and not the number, severity, proximal extent, or severity of GER.[89] In fact, most patients who had a clear temporal relationship between reflux and cough did not have pathologic levels of reflux. Therefore, it is not surprising that multiple clinical trials have failed to find a clear benefit of acid suppressive therapy in chronic cough,[90] in contrast to agents like gabapentin targeting neuronal sensitization, which have proven effective.[91]

REVISITING MECHANISMS OF GER: THORACOABDOMINAL MECHANICS

Given that GER is prevalent in respiratory disorders, it is reasonable to challenge the notion that reflux is somehow causal in all these quite disparate respiratory disorders. Thus, another hypothesis might be that respiratory dysfunction itself alters the esophageal function, promoting reflux. The abdomen and thoracic cavities are interdependent compartments separated by a highly dynamic divider, the diaphragm. It is easy to speculate how changes in the thoracic cavity from an underlying respiratory disorder could mechanically alter the abdominal compartment and promote GER. Unfortunately, very few physiologic studies have directly assessed the mechanical derangements associated with lung disease on GER.

Anatomically, there are key differences between the abdominal and thoracic compartments. The abdomen is a more compliant compartment that can transmit external pressures, such as with obesity, pregnancy, or abdominal muscle contraction, directly to the

intragastric pressure. Intragastric pressure may be increased directly due to delayed gastric emptying and dietary behavior (eg, excessive gastric volume/distention).[92-94] In contrast, the thoracic cavity is a more rigid structure with a negative pleural pressure during most of the inspiratory cycle, which is typically reflected and measured from the esophagus. The difference between these 2 pressures (gastric and esophageal) is the TDPG and can be loosely considered the prerequisite driving pressure that is required for GER to occur. There is some supportive data that gastric and esophageal pressures, and thus the TDPG, are known to vary with the respiratory cycle with voluntary maneuvers, exercise, coughing, and respiratory pathology (eg, obstructive and restrictive lung disease).[60,95-101]

Even with a significantly increased TDPG potentially promoting reflux, GER will not occur unless the intragastric pressure is able to breach the EGJ complex.[60] Although the LES has been the target of classic physiologic studies on reflux, is important to note that the EGJ complex comprises both the LES, under the influence of the vagus nerve,[102,103] and the striated diaphragmatic crural muscle, under the influence of the phrenic nerve.[7,95,102,104-106] This may be the anatomic basis for why respiratory disease could hinder the competency of the EGJ complex and further facilitate reflux. For example, obstructive disorders are marked by air trapping and hyperinflation, which secondarily flatten and caudally displace the normally dome-shaped diaphragm and potentiate the misalignment of the crural diaphragm and the LES. Notably, this process may not always be evident in static testing as measured during a pulmonary function test, and the process of *dynamic hyperinflation* may be evident only during formal cardiopulmonary exercise testing.[107-110] Furthermore, the crural diaphragms are likely subject to the same skeletal muscle dysfunction noted in patients with COPD, likely further contributing to a dysfunctional EGJ complex.[111] In contrast, lung volumes are contracted with advancing fibrotic lung disease and may displace the crural diaphragm upward, predispose patients to hiatal hernias,[104,105,112,113] and again compromise the EGJ competency.

Thus, during the dynamic process of respiration, particularly in the altered physiology and anatomy of restrictive and obstructive ventilatory disorders, it is plausible that some combination of an increased gastroesophageal pressure gradient[101] and a dysfunctional EGJ could facilitate GER. This hypothesis plausibly questions the causality assumption of whether GER is driving respiratory disease and would have major management implications, steering more away from treatment of GERD and more toward the fundamental physiologic derangements. Factors confirming that such interventions are possible include literature supporting the effect of inspiratory muscle training on improving the EGJ competency.[114,115] Additional targets for consideration include reducing transient LES relaxation events with baclofen analogues, improving esophageal motility, and potentially augmenting protective reflexes (swallow function, cough reflex) to mitigate against reflux-associated microaspiration. Additional mechanistic investigations are needed to clarify and confirm whether these hypothetical mechanisms are important.

CONCLUSION

Although GER is a prerequisite for gastric microaspiration, multiple protective factors must also be considered before it can be assumed to be a cause of or an aggravating factor for a patient's respiratory disease. Mechanistic studies enhancing our understanding of why GERD is prevalent across disparate respiratory disorders and how it interacts with respiratory mechanics to contribute to respiratory disease remain scarce. As gastric acidity is not the sole pathogenic agent of aspiration, these additional systematic investigations, utilizing comprehensive esophageal and respiratory function testing combined with evolving microaspiration biomarkers, should help to identify more effective targets of intervention.

Abbreviations and Acronyms: **ARDS** = acute respiratory distress syndrome; **BALF** = bronchoalveolar fluid; **CF** = cystic fibrosis; **COPD** = chronic obstructive pulmonary disease; **EGJ** = esophagogastric junction; **GER** = gastroesophageal reflux; **GERD** = gastroesophageal reflux disease; **IPF** = idiopathic pulmonary fibrosis; **LES** = lower esophageal sphincter; **PPI** = proton pump inhibitor; **TDPG** = transdiaphragmatic pressure gradient

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