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REVIEW ARTICLE

The Pulmonary Side of Reflux Disease: from Heartburn to Lung Fibrosis

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Abstract
Introduction Gastroesophageal reflux disease (GERD) is the most prevalent gastrointestinal disorder in the USA. Heartburn is the symptom most commonly associated with this disease, and the highly commercialized medical treatment directed toward relief of this symptom represents a 10-billion-dollar-per-year industry.
Discussion Unfortunately, there is often little awareness that GERD can be potentially a lethal disease as it can cause esophageal cancer. Furthermore, there is even less awareness about the relationship between GERD and respiratory disorders with the potential for severe morbidity and even mortality.

Keywords Gastroesophageal reflux disease · Lower esophageal sphincter · Esophageal peristalsis · Hiatal hernia · Obesity · Esophageal manometry · Ambulatory pH monitoring · Idiopathic pulmonary fibrosis · Lung transplantation · Laparoscopic Nissen fundoplication

Introduction

About 20 % of the US population experiences symptoms suggestive of gastroesophageal reflux disease (GERD), and this is the most common gastrointestinal disease process evaluated every day by primary care physicians.[1] Heartburn is the most common complaint, and it is usually treated with acid reducing medications such as H_2 blocking agents and proton pump inhibitors (PPIs) without confirmative diagnostic studies. This therapeutic approach is based on the assumption that symptoms are sensitive and specific for the diagnosis and on the consideration that diagnostic studies are invasive and expensive. However, this approach has several pitfalls. First, it has been shown that symptoms are a poor indicator of the reflux status. For instance, Patti et al. previously showed that among 822 patients with a diagnosis of GERD, the ambulatory pH monitoring was normal in 30 % of the patients.[2] Patients were labeled as having GERD and the real cause for their symptoms was initially overlooked. Irritable bowel syndrome, gallbladder disease, achalasia, and coronary artery disease can also manifest with heartburn.[2] Second, acid reducing medications are quite expensive and potentially dangerous because of their side effects.[1,3] More than 10 billion dollars are spent every year for PPIs, and two of the available PPIs are among the top five selling medications in the USA.[1] Although PPIs overall carry a good safety profile, adverse effects such as fractures related to osteoporosis, cardiac arrhythmias secondary to hypomagnesemia, diarrhea secondary to *Clostridium difficile*, and pneumonia have been described with increased frequency, particularly with prolonged use of these medications.[3] These observations stress the need for obtaining a secure diagnosis before prescribing these medications, avoiding their indefinite use, and selecting patients who might be better treated with a laparoscopic antireflux operation (Table 1).

Both on the part of the public and some members of the medical community, there is often the belief that heartburn is the major problem of GERD. There is little awareness that GERD can cause severe morbidity and even mortality. It is

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Table 1 Evaluation for gastro-esophageal reflux disease

Symptomatic evaluation
Barium swallow
Endoscopy
Esophageal manometry
Ambulatory pH monitoring
Combined multichannel intraluminal impedance and pH testing (MII-pH)

recognized today that adenocarcinoma of the esophagus is the end result of a sequence of events whereby about 10 % of patients with GERD develop Barrett's metaplasia, and about 0.5 to 1.0 % eventually progress to high-grade dysplasia and adenocarcinoma.[4,5] There are almost 18,000 new cases of esophageal cancer every year in the USA (about 90 % are adenocarcinomas), and the overall 5-year survival is about 20 %.[6]

Unfortunately, there is even less awareness about the relationship between GERD and respiratory disorders. Often patients with respiratory symptoms are labeled as having cough of unknown origin with GERD rarely considered in the differential diagnosis, even when typical symptoms such as heartburn and regurgitation are present. In addition, in patients with respiratory symptoms, esophageal manometry and pH monitoring are rarely performed to rule out the presence of silent reflux. Today, however, there is mounting evidence that GERD may play a role in the pathogenesis of many respiratory disorders and in particular in idiopathic pulmonary fibrosis (IPF), a lethal disease which affects about 34,000 newly diagnosed individuals every year.[7,8] IPF is an idiopathic chronic and progressive form of usual interstitial pneumonia on histopathology leading to lung fibrosis. Clinically IPF is characterized by dyspnea and a non-productive cough. Radiologically IPF is characterized by reticular fibrotic changes and a honeycomb pattern with multiple cystic spaces at the bases. The definitive diagnosis of IPF is established by exclusion of other causes of interstitial lung disease, a high-resolution computed tomography scan consistent with the diagnosis, and when available by a lung biopsy showing the typical histopathologic changes. This disease is progressive and irreversible. The median survival after diagnosis is between 3 to 5 years, with a 5-year survival of approximately 20 %. About 80 % of all deaths in IPF patients are secondary to respiratory failure.[8] Because medical therapy with anti-inflammatory, immunosuppressive, and anti-fibrotic medications has proven to be ineffective,[9] lung transplantation offers the only chance for increased survival. However, recent studies have suggested that this disease might not be as idiopathic as previously thought and that GERD, by causing micro-aspiration, might be one of the causative factors.[10–12] This manuscript reviews the available information linking GERD to pulmonary diseases, specifically trying to explain how a disease such as GERD can cause pulmonary fibrosis.

GERD: Definition and Pathogenesis

Multiple attempts have been recently made to define GERD.[13,14] Of the many consensus conferences, two in particular have had a significant impact. The Montreal consensus conference defined GERD "……as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications".[13] The Brazilian consensus conference instead defined GERD "….as a chronic disorder related to the retrograde flow of gastro-duodenal contents into the esophagus and/or adjacent organs, resulting in a variable spectrum of symptoms, with or without tissue damage".[14] We feel that the latter definition more accurately characterizes GERD, as it stresses its chronicity and underlines that the refluxate has both duodenal and gastric components. Both definitions, however, do not stress that the pathophysiology of GERD is multifactorial. This is of key importance to properly diagnose and treat this disease (Fig. 1).

Lower Esophageal Sphincter

The lower esophageal sphincter (LES) is about 3 to 4 cm in length, and it is composed of smooth muscle. Because the LES is tonically contracted, it creates a pressure zone between the stomach and the esophagus. It was initially thought that the *mechanical* characteristics of the LES determined its competence. Specifically, the LES was considered competent if it had a total length of at least 2 cm, an abdominal length of more than 1 cm, and a resting pressure of more than 6 mmHg.[15] However, this model was not able to explain why some patients had reflux in the presence of a mechanically competent LES. It became eventually evident that the most common cause of reflux was *functional* in nature and specifically due to the so-called transient LES relaxation (TLESR).[16] TLESR is as sudden loss of LES pressure not preceded by swallowing. Gastric distension has been shown to cause TLESR through a vago-vagal reflex.[17]

Diaphragm

The esophageal crus of the diaphragm plays an important role in the anti-reflux mechanism as it has a synergistic action with

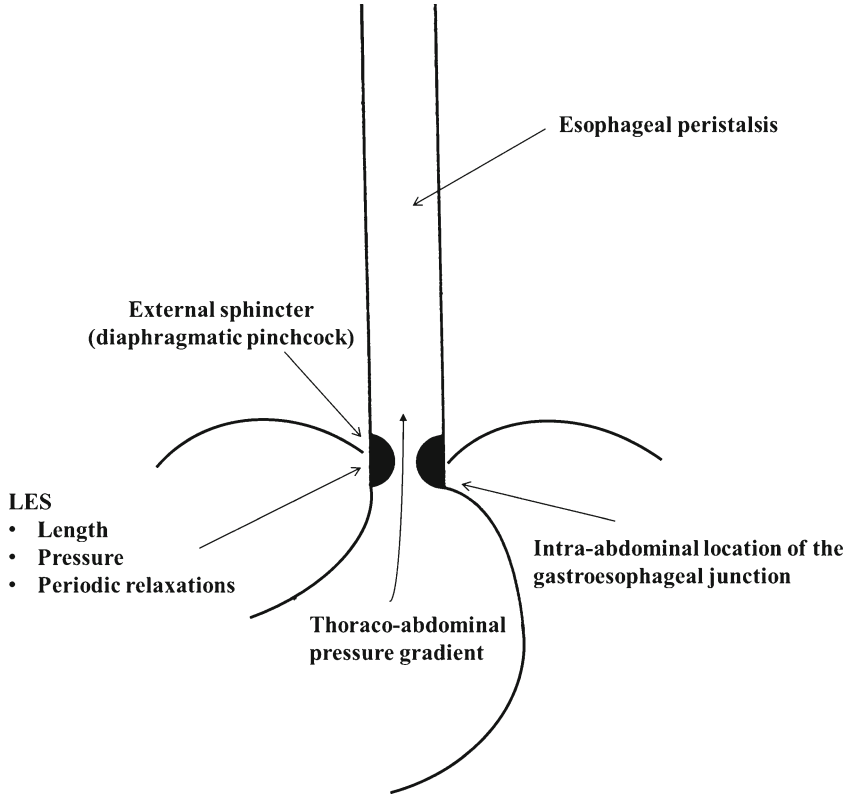

Fig. 1 Pathophysiology of gastroesophageal reflux disease

the LES. The crus works as an extrinsic sphincter, and this action is particularly important in preventing gastroesophageal reflux caused by sudden increases in abdominal pressure such as those that occur during coughing or bending. This synergism is lost in the presence of a hiatal hernia, as the gastroesophageal junction moves above the diaphragm. It has been shown that the presence and size of a hiatal hernia cause significant changes in esophageal physiology.[18,19] Patti et al. showed that the presence of a large hiatal hernia was associated with a shorter and weaker LES and decreased amplitude of esophageal peristalsis.[18] As a consequence, there was an increase in the frequency and duration of the reflux episodes and a slower acid clearance. In that study, patients with a large hiatal hernia often complained of respiratory symptoms such as cough and wheezing and had more severe esophagitis.

Thoraco-abdominal Pressure Gradient

The LES is a valve positioned in between two compartments, the abdomen with a positive pressure and the chest with a negative pressure. Because the stomach and the esophagus reflect the pressure of these two compartments, a natural gradient exists that favors reflux from the stomach into the esophagus. In normal conditions, the tonically active status of the LES prevents reflux from occurring.[20] However, an increase in the thoraco-abdominal pressure gradient can cause reflux even in the presence of a normal LES. Respiratory disorders associated with an increased ventilator effort can cause an even more negative intrathoracic pressure and a more positive intra-abdominal pressure by flattening of the diaphragm, thereby increasing the thoraco-abdominal gradient.[21] In addition, the thoraco-abdominal pressure gradient can be altered by an increase in the intra-gastric pressure as seen in obesity.[22,23] Herbella and colleagues showed that there was a linear correlation between obesity and reflux. Specifically, for every five points increase in the body mass index (BMI), there was a rise in the reflux score of 2.95 as measured by ambulatory pH monitoring.[22] In obese patients, reflux occurred in the presence of a normal or hypertensive LES. Pandolfino and colleagues explained this observation by showing that obese subjects are more likely to have an increased intra-gastric pressure, a greater thoraco-abdominal pressure gradient, and a more frequent separation of the LES and the diaphragmatic crus (with consequent hiatal hernia formation), as compared to subjects with a normal BMI.[23]

Esophageal Peristalsis

Esophageal peristalsis is a key component of the antireflux mechanism as it is the main determining factor for esophageal clearance of the gastric refluxate. Effective bolus clearance requires contractions with minimal amplitude of 30 mmHg in the distal esophagus.[24] Among 1,006 patients with GERD proven by ambulatory pH monitoring,

Diener and colleagues found that the peristalsis was normal in only 56 % of patients.[25] Among the patients with abnormal peristalsis, 21 % had a severe disorder characterized by amplitude of less than 30 mmHg in the distal esophagus and by non-transmitted contractions after more than 30 % of swallows.[25] This disorder, classified as ineffective esophageal motility, is associated with slower acid clearance, more severe mucosal injury, and frequent respiratory symptoms.[25,26] It is unclear if this motor abnormality is a primary phenomenon or secondary to GERD. However, some studies have shown normalization of peristalsis after complete control of reflux by fundoplication, suggesting that the altered motility is probably a consequence of the abnormal reflux.[27]

Refluxate

Because it is usually thought that the symptoms and the esophagitis that characterize GERD are due to the reflux of acid from the stomach into the esophagus, therapy has been based on medications that block the production of acid by the gastric parietal cells. However, acid is just one component of the refluxate; duodenal contents containing bile salts and pancreatic enzymes play an important role in the genesis of reflux symptoms and in the severity of the mucosal damage. This was clearly shown by Kauer and colleagues who studied simultaneously acid reflux (by conventional pH monitoring) and duodenal juice reflux (by a sensor for bilirubin) in 53 patients with GERD.[28] They found that about two third of patients had a mixed form of reflux and that patients with Barrett's metaplasia had a greater exposure to bilirubin as compared to patients without. These findings explained why some patients have only partial control of symptoms with PPI therapy and why others have an increased risk of developing Barrett's esophagus.[28] The therapeutic implications are obviously very important. Different studies using intraluminal impedance technology have shown that PPIs just change the pH of the gastric refluxate because of the reduced production of acid, but reflux persists if the LES is incompetent.[29] Ambulatory impedance pH monitoring clearly identifies the relationship between typical and atypical symptoms and reflux episodes, both acid and non-acid.[30] And when non-acid episodes of reflux are thought to be the cause of symptoms, a fundoplication is more effective than PPIs, as it is able to restore the competence of the gastroesophageal junction, therefore blocking any type of reflux.[31]

Establishing the Link Between the Esophagus and the Lung

Many studies in the 1960s and 1970s proposed a possible correlation between GERD and respiratory disorders such as asthma, bronchitis, and pneumonitis, and some even suggested a possible cause and effect relationship between hiatal hernia, reflux, and pulmonary fibrosis.[32,33] In 1976, Mays suggested that IPF might not be due to a viral insult or to an autoimmune disease but rather to lung damage secondary to aspiration in patients with gastroesophageal reflux and a hiatal hernia.[33] Interestingly, it has taken decades to demonstrate the validity of this theory and to establish a link between the esophagus and the lung.

In 1979, Pellegrini et al. described the incidence of pulmonary aspiration and its underlying pathophysiology in 100 patients with GERD documented by ambulatory pH monitoring of the distal esophagus. The pH probe was positioned 5 cm above the upper border of the manometrically determined LES.[34] They identified eight patients as aspirators because they had reflux in the distal esophagus temporally followed by acid taste in their mouth with cough or wheezing. In these patients, esophageal manometry showed the presence of abnormal peristalsis, and pH monitoring showed slower acid clearance in the supine position as compared to patients with GERD but no respiratory symptoms.[34] They concluded that in some patients with GERD and abnormal peristalsis, acid can reflux all the way upward, eventually spilling into the tracheobronchial tree. However, it is important to recognize that because acid reflux was measured in the distal esophagus only, the authors postulated but did not show that reflux actually extended to the upper esophagus and pharynx.[34]

Years later, Johnson et al. studied the role of reflux in 13 patients with systemic sclerosis, as a contributing factor to the pulmonary problems of these patients.[35] In addition to endoscopy (with biopsies of the distal and proximal esophageal mucosa), pulmonary function tests, and esophageal manometry, patients underwent a 24-h pH monitoring with two probes positioned 5 and 15 cm above the LES. This study showed that in 77 % of patients, no peristalsis was present and that in some patients, acid extended all the way to the upper esophagus (by biopsies of the upper esophageal mucosa and/or reflux episodes recorded by the proximal pH probe). This study suggested that chronic aspiration of gastric contents may contribute to the pulmonary complications of systemic sclerosis.[35] The applicability of the findings of this study to the average patient with GERD is, however, limited by the fact that patients with systemic sclerosis often have an end-stage form of esophageal disease characterized by complete absence of peristalsis.

In 1993, Patti and colleagues prospectively studied 70 patients with GERD referred for evaluation of symptoms of gastroesophageal reflux.[36] The following questions were asked: Does reflux extend to the proximal esophagus? And if this is the case, what is the underlying pathophysiology and what is the clinical presentation of patients with proximal reflux? After review of the pH monitoring studies, two

groups of patients with abnormal gastroesophageal reflux (GER) were identified: group A (pH<4 in the proximal esophagus <3 %, GER) and group B (pH<4 in the proximal esophagus ≥ 3 %, high-GER). Symptomatic evaluation, esophageal manometry, and ambulatory pH monitoring were performed in all patients. For the first time, pH monitoring was performed with one probe containing two antimony sensors, which were positioned 5 and 20 cm above the LES (Fig. 2). This study showed that in a subgroup of patients with abnormal GER, a pan-esophageal motor disorder was present, characterized by a short and hypotensive LES and ineffective esophageal peristalsis. As a consequence, acid clearance was slower and the upper esophagus was exposed to acid for a longer period of time. Because of the abnormal motor function and abnormal reflux profile, patients with high-GER complained more frequently of symptoms suggestive of aspiration such as cough and wheezing and had a history of pneumonia (Table 2).

Wilshire and colleagues recently studied the association between episodes of reflux and oxygen desaturation, as a way to identify patients whose respiratory symptoms are due to reflux by using simultaneous 24 h pH impedance and pulse oximetry monitoring.[37] They showed that there was a relationship between episodes of reflux in the distal and proximal esophagus and episodes of desaturation and that antireflux surgery decreased these events.

Even though all these studies strongly suggested that respiratory symptoms could be due to aspiration, they were still lacking the final proof, i.e., showing gastric contents in the tracheobronchial tree. Eventually this link was established by determining the presence of pepsin in the bronchoalveolar lavage fluid (BALF), as a marker of gastric contents in the tracheobronchial tree.[38–42] Pepsinogen is released by the gastric chief cells and is converted to pepsin by the hydrochloric acid produced by the parietal cells. Because pepsin is normally absent from the esophagus and the respiratory tract, it represents a useful marker of aspiration of gastric contents. Farrell et al. were the first to use a pepsin immunoassay of the BALF to investigate reflux related aspiration in children with a GERD proven by pH monitoring.[42] They showed that the concentration of pepsin in the BALF was elevated in children with cough and proximal reflux, confirming that aspiration was occurring. Alternatively, aspiration of gastric contents can be proven by the identification of bile acids in the BALF.[43]

From GERD to IPF and Beyond

IPF is an interstitial lung disease characterized by aberrant fibroblast proliferation which is felt to be secondary to recurrent epithelial injury. The etiology is unknown, as the initial insult causing this process of fibrosis has never been identified. It has been suggested that abnormal reflux may play a role in the pathogenesis and in the progression of this disease, an exciting hypothesis considering that GERD can be easily treated.[33,44–48]

Thirty-seven years ago, Mays showed that among 48 patients with IPF, the prevalence of a hiatal hernia and reflux was two times higher than in patients with a known cause of fibrosis.[33] More recently, in a case–control study of more than 200,000 US Veterans, El-Seraq and Sonnenberg showed that individuals with erosive esophagitis had a 1.36 odds ratio of pulmonary fibrosis.[44]

Noth and colleagues studied the prevalence of hiatal hernia by computerized tomography in 100 patients with IPF and compared the findings to 60 patients with COPD and 24 patients with asthma.[45] They found that a hiatal hernia was more common in IPF patients (39 %) than in COPD (13 %) or asthma patients (17 %). In addition, they showed that the presence of a hiatal hernia correlated with reflux as measured by ambulatory pH monitoring.

Furthermore, recent studies in IPF patients awaiting lung transplantation have shown a very high prevalence of distal and proximal reflux when measured by pH monitoring.[46–48] Sweet and colleagues studied 27 IPF patients awaiting lung transplantation, with dual probe pH monitoring, and found abnormal distal reflux in 78 % and proximal reflux in 33 % of them.[46] Similar findings have been documented by others.[47,48] In addition, aspiration of gastric contents (as shown by pepsin documented in the BALF) may play a role in some cases of acute exacerbation of IPF, a sudden worsening of the respiratory status that leads to substantial morbidity and mortality.[49]

Taken all together, these data support the hypothesis that reflux is at least an important contributor to the epithelial injury that leads to lung fibrosis and to the progression of the disease. And because there is no effective therapy for IPF, it makes sense to treat the abnormal reflux by a well-proven therapy for GERD, a laparoscopic fundoplication. It is known that a total fundoplication is the anti-reflux procedure of choice, as it controls reflux in more than 90 % of patients with a secure diagnosis of GERD and its efficacy lasts overtime.[50–52] This procedure provides excellent control of abnormal reflux as it addresses multiple aspects of the pathophysiology of GERD. A fundoplication eliminates the hiatal hernia by reducing the gastroesophageal junction below the diaphragm, therefore restoring the pinchcock action of the esophageal crus[51] In addition, it increases the pressure and length of the LES, decreases the number of transient LES relaxations, and improves esophageal peristalsis.[52–54] The operation has a great safety profile, and it can be performed with minimal morbidity and mortality both in young and elderly patients, with equally excellent outcomes.[55]

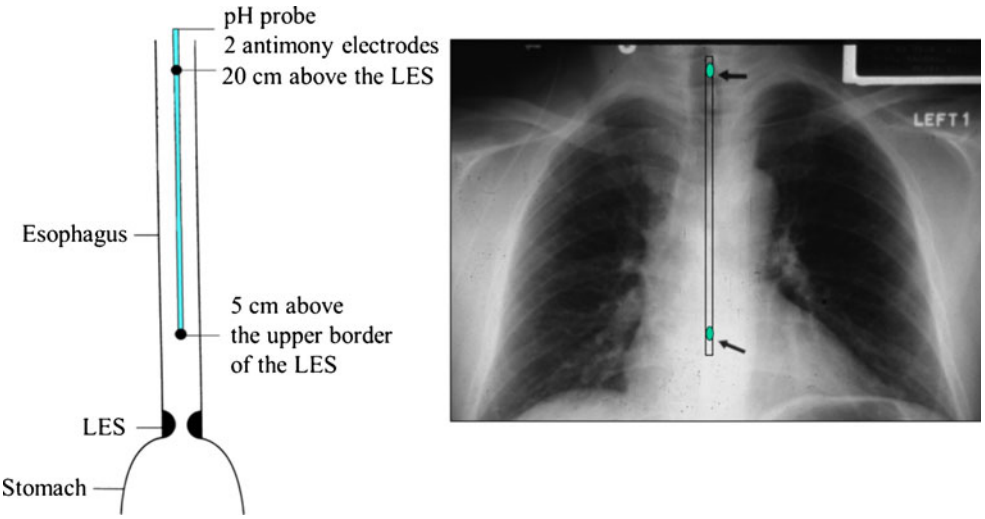

Fig. 2 24-h ambulatory pH monitoring with dual sensor probe

Antireflux surgery has been used to treat respiratory symptoms thought to be secondary to aspiration in patients with GERD.[34,56–58] For instance, Pellegrini et al. performed a Nissen fundoplication in five patients with cough secondary to aspiration and noted complete resolution of the symptom in all patients.[34] Hunter et al. observed improvement or resolution of respiratory symptoms in 87 % of patients after fundoplication.[57] Patti et al. showed that after laparoscopic fundoplication, respiratory symptoms improved in 83 % (19 of 23 patients) when a temporal correlation between cough and episodes of acid reflux was established by pH monitoring.[58] A laparoscopic Nissen fundoplication is also effective in resolving respiratory symptoms due to non-acid reflux.[59]

Furthermore, some recent exciting data also support the use of fundoplication in the management of patients with IPF and GERD. For instance, Linden et al. performed a fundoplication in 14 patients with IPF and GERD and compared the outcome to that of 31 patients with IPF who did not have the fundoplication as a control group.[60] Over the 15-month follow-up period, there was stabilization of the oxygen requirement in patients who had the fundoplication while the requirement increased significantly in the control group. Recently Hoppo et al. reported on 19 pre-lung transplant patients with GERD and end stage lung disease who had an antireflux operation.[61] One year after the operation, there was an improvement in the forced expiratory volume in 1 s (FEV1) in 85 % of patients. In addition, they did not experience an increase in the number of episodes of pneumonia. These observations have also been confirmed by a retrospective study of 204 IPF patients treated at the University of California San Francisco and

Table 2 Clinical and functional characterization of high gastroesophageal reflux

	Patients with GER	Patients with high-GER	*p* value
Symptoms (% patients)			
Heartburn	90	57	0.008
Dysphagia	27	64	0.008
Cough and/or wheezing	27	68	0.003
History of pneumonia	0	27	0.001
24-h pH monitoring			
Proximal % time pH<4	0.8±0.9	11.5±6.7	0.001
Distal % time pH<4	9.2±12.8	29.8±22.6	0.001
Proximal acid clearance (min)	0.5±0.4	5.7±5.8	0.001
Distal acid clearance (min)	1.6±1.5	8.8±10.2	0.001
Esophageal manometry			
LES total length (cm)	2.2±0.7	1.5±0.5	0.001
LES pressure (mmHg)	13.5±6.0	7.8±4.6	0.001
Proximal wave amplitude (mmHg)	59.2±17.6	42.4±18.0	0.001
Distal wave amplitude (mmHg)	89.7±25.2	54.7±27.9	0.001
% simultaneous waves	3.1±9.7	22.7±33.6	0.001
UES pressure (mmHg)	73.7±30.7	54.7±29.3	0.017

GER gastroesophageal reflux, *LES* lower esophageal sphincter, *UES* upper esophageal sphincter

the Mayo clinic in Rochester. The study showed that a history of laparoscopic fundoplication was an independent predictor of longer survival.[62] Medical therapy (mostly with PPIs) was less effective.

Overall, a definitive answer can only be given by a prospective, randomized trial comparing survival in IPF patients with GERD treated by either a laparoscopic fundoplication or no antireflux medications. Until then, this operation should only be performed in selected IPF patients whose functional status does not preclude general anesthesia and in centers where a skilled laparoscopic foregut surgeon is part of an experienced multidisciplinary team.[63]

Most patients with IPF experience a progressive deterioration, and because medical therapy is largely ineffective in blocking the progression of the disease and eventually death, lung transplantation remains the only viable option for survival.[64,65] However, this treatment has several drawbacks. First, few organs are available. Second, in about 50 % of cases, both lungs are transplanted into the same patient. This is a demanding operation with considerable morbidity and mortality.[66] Third, different from other solid organ transplants like heart and kidney which have a 5-year survival of approximately 80 %, the 5-year survival after lung transplant is only 50 %.[66] Forth, in addition to other common causes of death after transplantation such as infection, most patients after lung transplant develop a process of fibrosis of the small airways known as *bronchiolitis obliterans*.[67] The clinical correlate is the so-called *bronchiolitis obliterans syndrome* (BOS), a progressive deterioration of the lung function as measured by the decline of the FEV1 after transplant. BOS is responsible for approximately 50 % of deaths beyond the first year after the lung transplant.[67] It was initially believed that BOS was due to immune factors. However, because it soon became evident that its very high rate persisted despite advancement in immunotherapy, other causes were sought. Today it has been shown that aspiration of gastroduodenal contents is common after lung transplantation and that it can be one of the triggers that cause the pulmonary injury that leads to BOS. Both pepsin and bile acids have been found in the BALF of patients after lung transplantation.[43,68–70] While pepsin is usually considered just a marker of aspiration,[68,69] bile acids might promote BOS via an inflammatory process mediated by IL-8 and alveolar neutrophilia.[43] In addition, bile acids can cause impairment of the lung allograft immunity by affecting pulmonary surfactant, collectin proteins, and phospholipids.[70] Many studies have confirmed that a laparoscopic fundoplication can be performed safely in patients after lung transplantation, with a complication rate similar to that of patients with GERD but no IPF.[63,71–74] In addition, it is effective in controlling aspiration, as determined by the levels of pepsin in the BALF measured before and after the fundoplication.[69] Finally, it has been shown that a laparoscopic fundoplication protects against the development of BOS, particularly when performed early after the lung transplant.[72,73] Importantly, to support the pathogenetic role of GERD in IPF, we have shown that lung transplant patients with IPF had higher BALF pepsin concentrations and a greater frequency of acute rejection compared to those with chronic obstructive pulmonary disease, cystic fibrosis, and α_1-anti-trypsin deficiency.[75] Moreover, our group has also shown that BALF levels of IL-15, IL-17, bFGF, TNF-α, MPO, and α_1-anti-trypsin deficiency at 6–12 months after lung transplantation are predictive of early-onset BOS, and those with BOS and aspiration have an augmented chemotactic and inflammatory balance of pulmonary leukocytes and immune mediators.[75]

Conclusions

Overall there is mounting evidence linking GERD not only to cancer of the esophagus but also to another potentially lethal disease, IPF. As physicians, we have the unique opportunity to identify early the role-played by GERD in the pathogenesis of these diseases and to prevent the cascade of events that ultimately may lead to death (Fig. 3).

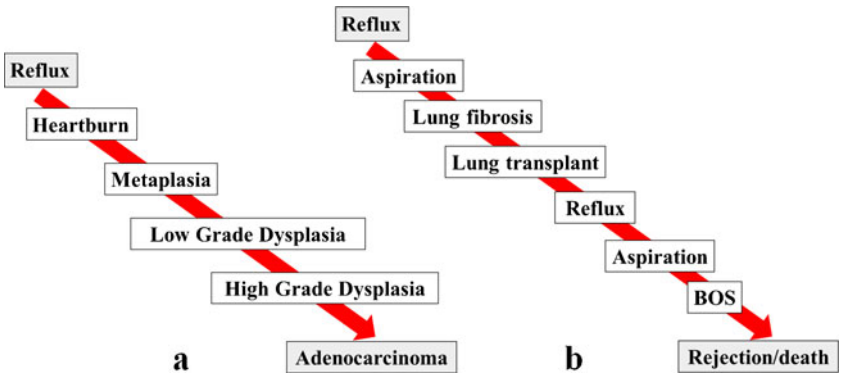

Fig. 3 The evolution of gastroesophageal reflux disease. **a**. From heartburn to cancer. **b** From heartburn to lung fibrosis, and beyond

Conflict of Interest The authors have no conflict of interest.

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