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SURGICAL SYMPOSIUM CONTRIBUTION

Gastroesophageal Reflux and Idiopathic Pulmonary Fibrosis

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown origin that affects about 40,000 new patients every year in the USA. Albeit the disease is labelled as idiopathic, it is thought that pathologic reflux, often silent, plays a role in its pathogenesis through a process of microaspiration of gastric contents.

Aims The aim of this study was to review the available evidence linking reflux to IPF, and to study the effect of medical and surgical therapy on the natural history of this disease.

Results Medical therapy with acid-reducing medications controls the production of acid and has some benefit. However, reflux and aspiraion of weakly acidic or alkaline gastric contents can still occur. Better results have been reported after laparoscopic anti-reflux surgery, as this form of therapy re-establishes the competence of the lower esophageal sphincter, therefore stopping any type of reflux.

Conclusions A phase II NIH study in currently in progress in the USA to determine the role of antireflux surgery in patients with GERD and IPF. The hope is that this simple operations might alter the natural history of IPF, avoiding progression and the need for lung transplantation.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and irreversible interstitial pneumonia of unknown origin that affects approximately 38,000 individuals every year in the USA [1]. It progressively leads to lung fibrosis, respiratory failure, and eventually to death [2].

Even though the etiology of IPF is still unclear, the lung exposure to factors that might cause injury to the pulmonary parenchyma inducing an inflammatory response and subsequent fibrosis has been suggested to be key for the development of the disease. Chronic microaspiration of gastric refluxate might be one of these insulting factors involved in the pathogenesis of IPF [3]. GERD is much more prevalent in IPF patients than in the general population, in patients affected by cystic fibrosis, asthma, or chronic obstructive pulmonary disease [4–9]. In addition, a laparoscopic fundoplication in the management of patients with IPF and GERD has been reported to both control reflux and avoid aspiration of refluxate, thus slowing the progression of this disease [10–12]. Finally, a role of proton pump inhibitors (PPI) slowing down the impairment of lung function, decreasing the number of episodes of acute exacerbation of the disease and prolonging the transplant-free survival has been shown in IPF patients [13].

This manuscript reviews the current knowledge available on the relationship between IPF and GERD, focusing on clinical presentation, esophageal motility and reflux profile of patients with IPF. The effects of both acid

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suppressing therapy and anti-reflux surgery in patients with IPF are also discussed.

GERD and IPF: clinical presentation and gastroesophageal function

Symptoms

While heartburn and regurgitation are the most common symptoms reported by GERD patients without IPF, reflux is often asymptomatic in GERD patients with IPF. A study from the University of Chicago evaluated the clinical presentation in 80 patients with GERD only and in 22 patients with GERD and IPF [14]. The prevalence of heartburn was significantly lower in patients with IPF than in patients with GERD only (59 vs. 84%, $P = 0.028$), while the two groups did not differ in terms of prevalence of regurgitation. Extra-esophageal manifestations of GERD, including hoarseness, cough and chest pain were significantly more common among patients with IPF. Duration of symptoms was also similar in the two groups. These results are consistent with those reported by other authors [4, 15–17]. For instance, Sweet et al. [16] determined the prevalence of reflux symptoms in 109 patients awaiting lung transplantation for end-stage lung disease (27 patients with IPF). All patients underwent esophageal manometry and ambulatory 24-pH monitoring. A total of 74 patients had pathologic reflux, while 35 had a normal 24-pH study. The main symptoms were respiratory. Reflux was asymptomatic in 33% of those with distal reflux and in 38% of those with proximal reflux. At least one typical GERD symptom, such as heartburn, regurgitation, or dysphagia was reported by 69% of subjects. There was no difference in the prevalence and severity of heartburn or regurgitation among patients with and without GERD. Only half of the patients with GERD had dysphagia. There was no correlation between severity of typical symptoms, and the DeMeester score or the percentage of time the pH was <4.0 in the proximal esophagus. Moreover, the sensitivity and specificity of typical symptoms of GERD were 67 and 26%, respectively, for distal reflux, and 62 and 26%, respectively, for proximal reflux.

These findings show that typical symptoms do not allow to distinguish between patients with and without pathological reflux. Since abnormal reflux is silent in more than one-third of cases, 24-hour pH monitoring should be routinely obtained to screen these patients for GERD regardless of the absence of symptoms.

Esophageal manometry

The LES pressure is normal in most IPF patients, suggesting that transient LES relaxations (TLESR) rather than a mechanically defective LES represent the pathophysiological mechanism of abnormal reflux of gastric contents into the esophagus. On the contrary, the upper esophageal sphincter (UES) pressure is frequently lower in IPF patients and this might be associated with an increased risk of aspiration. Studies comparing GERD patients with or without IPF showed that the amplitude of esophageal peristalsis in both proximal and distal esophagus is not impaired in IPF patients: ineffective esophageal motility, that is frequently detected in patients with other lung diseases, is uncommon in patients with IPF [4, 14, 18]. In particular, Raghu et al. [4] found in an analysis of 65 IPF patients that mean LES length, pressure and percentage of relaxation were within the normal range, and the vast majority of patients had normal esophageal peristalsis. These pathophysiological findings lead to a tailored approach in patients with pulmonary disorders who are scheduled for anti-reflux surgery: while patients with connective tissue disorders more frequently undergo a partial fundoplication in order to minimize the risk of postoperative dysphagia, patients with IPF have a total fundoplication. There is evidence that a total wrap is associated with better reflux control than a partial wrap: it increases LES pressure, decreases TLESR and improves the amplitude of the esophageal peristalsis [19–27].

Reflux profile

Several studies using a dual-channel pH probe have reported frequent proximal reflux events in IPF patients, with pathological proximal esophageal acid exposure to acid refluxate in up to two-thirds of patients [4, 28, 29]. For instance, Raghu et al. [4] studied the reflux profile in 65 consecutive IPF patients with 24-hour pH monitoring. Overall prevalence of pathological reflux was 87%, and only 47% of these patients were symptomatic for reflux. Among the 46 (71%) IPF patients who were not taking PPIs at the time of the pH monitoring, the prevalence of pathologic distal and proximal esophageal acid exposure was 76 and 63%, respectively. Recently, Hoppo et al. [30] analyzed the reflux profile in 28 IPF patients by using the 24-hour hypopharingeal multichannel intraluminal impedance (HMII): 15 patients had abnormal proximal exposure. Proximal reflux was defined as laryngopharyngeal reflux $\geq$1/day and/or full column reflux $\geq$5/day. About 25% of proximal reflux events were non-acid. These patients had a higher rate of esophageal mucosal injury, higher numbers of total and distal reflux events and a trend toward longer acid clearance time than the patients without abnormal proximal exposure. However, there were no significant differences in the clinical presentation, and the DeMeester score was within the normal values in more than 80% of patients in both groups. Further large studies

are needed to validate the routine use of HMII in the functional evaluation of patients with IPF.

The evidence coming from studies comparing GERD patients with or without IPF suggest that the total DeMeester score is usually not significantly different between the two groups of patients. However, the total esophageal acid exposure in the proximal esophagus is significantly higher in IPF patients. This difference is mainly detected in the supine position, while the acid exposure in the upright position is not significantly different. Similarly, total and supine acid clearances are significantly slower in IPF patients, while no significant differences are usually observed in the upright position [14].

Based on the recent detection of both pepsin and bile acids in the broncho-alveolar lavage fluid (BALF) [31] suggesting that both acidic and non-acidic reflux might be involved in the pathogenesis of IPF, some studies have studied the reflux profile in IPF patients by using multichannel intraluminal impedance and pH study (MII-pH), confirming that non-acidic refluxate occurs in these patients and may be involved in the pathogenesis of IPF [31, 32]. Further studies are needed to verify the role of MII-pH monitoring compared to ambulatory 24-pH monitoring in the assessment of patients with IPF.

GERD and IPF: is there a link?

The current knowledge about the link existing between GERD and IPF is the result of a 40-year long story that started in 1971 when Pearson et al. [33] described 6 patients with initially obscure pulmonary fibrosis that was then attributed to GERD. In addition, they reviewed further 143 consecutive patients with hiatal hernia and GERD, reporting pulmonary symptoms and radiographic changes of chronic pulmonary fibrosis in 6 (4%) patients. Five years later, Mays et al. [34] prospectively studied 48 patients with radiologic evidence of pulmonary fibrosis of unknown origin. Upper gastrointestinal series were obtained in these patients to assess the incidence of hiatal hernia and GERD. Both hiatal hernia and GERD were significantly more common in the study group than in a group of 270 age-matched controls who had upper gastrointestinal series for the usual indications, a group of 38 patients with immune-mediated PF or PF of established etiology. These findings supported the concept that IPF might be the result of repeated episodes of microaspiration of gastric acid secretions over a long period of time. However, there was no proof of an association between the onset of IPF and GERD.

Significant light on the possible association between GERD and pulmonary disorders was shed a few years later when a temporarily defined correlation between aspiration and esophageal acid exposure was found. In 1979, Pellegrini et al. [35] assessed the incidence of pulmonary aspiration and the esophageal pathophysiology in 100 patients with GERD diagnosed by ambulatory 24-pH monitoring with the pH probe that was positioned 5 cm above the upper border of the manometrically determined LES. Aspiration was suspected to occur in 48 GERD patients based on the reported symptoms. A total of 9 patients were considered to be potential aspirators because of reported oral acid regurgitation without developing pulmonary symptoms, while 8 patients were identified as aspirators according to the detection of reflux episodes in the distal esophagus temporally followed by acid taste in the mouth with cough or wheezing. In 75% of aspirators, esophageal peristalsis was abnormal and acid clearance in the supine position was slower than in patients with GERD and no respiratory symptoms. The results of this study showed for the first time a correlation between respiratory symptoms and GERD episodes, suggesting that in some GERD patients, acid contents might reflux all the way upward in the presence of impaired peristalsis, eventually causing respiratory symptoms.

However, since only acid exposure of the distal esophagus was measured, the authors were not able to show that refluxate extended to the upper esophagus and eventually spilled into the tracheobronchial tree. A major advancement in the understanding of the pathophysiology of reflux and possible links with pulmonary disorders was achieved 14 years later by the group of the University of California San Francisco. In 1992, Patti et al. [36] evaluated esophageal function and the presence of GERD in 23 consecutive patients with persistent respiratory symptoms of unexplained etiology. The relationship between reflux episodes and respiratory complaints was also assessed. For the first time, ambulatory 24-pH monitoring was obtained by using a probe with two antimony sensors that were positioned 5 cm and 20 cm above the LES. Aspiration was diagnosed when respiratory symptoms occurred during or within 3 min after a reflux episode. Based on these criteria, 12 patients were considered non-aspirators, while 11 patients were labeled as aspirators. Aspirators had a lower LES pressure, decreased peristalsis amplitude in both proximal and distal esophagus, and higher incidence of simultaneous, nonperistaltic waves and lower UES pressure. Impaired peristalsis in aspirators caused a higher acid exposure and delayed clearance in the proximal esophagus. These results demonstrated that, in patients with respiratory symptoms of unexplained origin, LES, peristalsis and UES are defective.

In 1993, the same group prospectively studied symptoms, esophageal manometric findings and ambulatory pH monitoring in 70 patients referred for evaluation of GERD

symptoms [15]. The aim was to evaluate the possible extension of reflux to the proximal esophagus, the underlying esophageal pathophysiology and the clinical presentation of patients with proximal reflux. The authors demonstrated the presence of a subgroup of patients with abnormal GERD, who have an esophageal motility disorder, characterized by ineffective esophageal peristalsis, and a short and hypotensive LES. The ambulatory 24-hour pH monitoring showed in these patients a slower acid clearance and a longer exposure of the proximal esophagus to acid refluxate. As a consequence of these esophageal dysfunctions, these patients reported more frequently symptoms suggestive of aspiration such as cough and wheezing, and had a history of pneumonia.

A further proof of a relationship between episodes of reflux and respiratory symptoms was recently provided by Wilshire et al. [37] in a study that included 37 patients with respiratory symptoms, 26 patients with typical symptoms, and 40 control subjects. All subjects underwent simultaneous 24-h impedance-pH and pulse oximetry monitoring, in order to evaluate the association between reflux events and oxygen desaturations in patients complaining respiratory symptoms thought to be secondary to GERD. Patients with respiratory symptoms had a significantly greater number of distal and proximal reflux events associated with oxygen desaturation than individuals with typical symptoms or control subjects.

Even though these studies supported the hypothesis that respiratory symptoms and proximal gastroesophageal reflux are linked and that microaspiration of refluxate might be one of the key factors in causing symptoms and eventually the onset and progression of pulmonary diseases, none of them provided the proof that microaspiration occurred in symptomatic patients. We had to wait the early 2000s to demonstrate the occurrence of microaspiration in GERD patients, by measuring pepsin and bile salts in the broncho-alveolar lavage fluid (BALF). Since both are not normally present in the esophagus and in the respiratory tract, they represent two useful biomarkers of aspiration of gastric and biliary contents. Krishnan et al. [38] first demonstrated in 2001 that tracheal pepsin assay is a reliable marker of aspiration. They evaluated 98 children undergoing general anesthesia and tracheal intubation: 64 children were symptomatic for GERD, while 34 children served as controls. These two groups were further subdivided based on the presence or absence of associated respiratory symptoms. Tracheal pepsin was found more frequently in children with GERD symptoms than in those without, particularly in children with both GERD and respiratory problems. Tracheal pepsin was not detected in any of the 26 children without GERD or respiratory symptoms. A few years later, Farrell [39] and Starosta [40] confirmed these findings, showing that children with cough and proximal reflux had significantly higher concentrations of pepsin in the BALF. Very recently, Davis et al. [41] measured pepsin in the BALF of 100 patients after lung transplantation for several chronic lung diseases, including IPF. They found that BALF pepsin levels were higher in IPF patients than in patients with α1-antitrypsin deficiency, cystic fibrosis, or chronic obstructive pulmonary disease. In addition, there was a negative correlation between BALF pepsin and upright acid clearance time.

GERD and IPF: what are the outcomes of PPI therapy and anti-reflux surgery?

The increasing evidence supporting the hypothesis that GERD plays a major role in the pathogenesis and progression of IPF and the lack of an effective therapy for IPF have promoted several studies aiming at investigating the outcomes of both anti-acid medications and anti-reflux surgery.

PPI therapy

Cell biological and preclinical studies [42] have shown that PPIs but not histamine H2-receptor antagonists act as scavengers of reactive oxygen species, induce the production of antioxidants, and suppress pro-inflammatory cytokines. In addition, PPIs inhibit the expression of pro-fibrotic molecules, including collagen, fibronectin and matrix metalloproteinase enzymes and significantly decrease lung epithelial cells apoptosis. During the last 10 years, several studies have reported several benefits of PPIs in IPF patients, including stabilized or improved lung function, less episodes of acute exacerbation and low rates of hospitalization for respiratory problems, prolonged transplant-free survival, and lower radiologic fibrosis score than controls [12, 43–45]. Based on these results, the 2015 updated evidence-based guideline for treatment of IPF recommended the use of anti-acid medications in IPF patients [46]. However, this evidence has been challenged by some recent controversial results. For instance, Kreuter et al. [47] in a post hoc analysis of 3 clinical trials including 624 IPF patients found that anti-acid therapy did not improve the outcomes and led to higher rates of pulmonary infections in the patients with a more advanced stage of disease. These mixed results might be due to the fact that PPIs do not stop reflux: PPIs only change the pH of the gastric refluxate, thus not preventing both acid and non-acidic gastric reflux and its microaspiration into the respiratory tract.

Anti-reflux surgery

A laparoscopic fundoplication is the treatment modality of choice for GERD, with very limited postoperative

morbidity and mortality and excellent long-lasting functional outcomes. Compared to anti-acid medications, anti-reflux surgery controls both acidic and non-acidic reflux and restores the anatomy of the gastroesophageal junction. The first evidence of the benefits of anti-reflux surgery in patients with respiratory symptoms secondary to aspiration was provided in the "open" era by Pellegrini et al. [35] who reported complete resolution of symptoms in 5 patients. Excellent results were obtained also with the laparoscopic approach in the early 2000s. For instance, Patti et al. [48] found cough resolution after laparoscopic fundoplication in 83% of patients presenting a temporal correlation between respiratory symptoms and acid reflux episodes detected by pH monitoring. A few years later, Ciovica et al. [49] studied the outcomes at 3 and 12 months after laparoscopic fundoplication in 126 patients with respiratory GERD-related symptoms. A significant improvement of all respiratory symptoms and quality of life was observed after surgery.

More recently, specific data about the outcomes of laparoscopic anti-reflux surgery in IPF patients became available, showing that anti-reflux surgery results in normalization of esophageal acid exposure and is characterized by a high profile of safety even in these frail patients. Linden et al. [10] in 2006 reported no perioperative morbidity and stationarity of the lung function over the 15-month follow-up period in 14 IPF patients, while 31 IPF patients who did not undergo anti-reflux surgery experienced significant increase in oxygen requirement. More recently, a retrospective multicenter study showed that a Nissen fundoplication was an independent predictor of survival in 204 IPF patients treated at the University of California San Francisco and Mayo Clinic [12]. Finally, a recent study by Raghu et al. [50] including 27 patients with progressive IPF undergoing laparoscopic fundoplication showed no postoperative 90-day mortality or acute exacerbation, minimal morbidity, a significant decrease in mean DeMeester scores after surgery, and a 2-year survival of 81.5%. The results of the ongoing prospective, multicenter and randomized phase II trial WRAP-IPF (Weighing Risks and Benefits of Laparoscopic Anti-reflux Surgery in Patients with Idiopathic Pulmonary Fibrosis—NCT 01982968) [51] are expected to validate the safety profile and the efficacy of laparoscopic Nissen fundoplication in IPF patients with acid GERD.

Conclusions

Silent pathologic reflux is highly prevalent in IPF patients. Microaspiration is considered one of the main factors leading to damage of pulmonary parenchyma. However, the presence of GERD does not imply microaspiration. The cause–effect relationship is today still unclear: is the chronic microaspiration of gastric contents the causative factor of onset and progression of the disease or does the reduced lung compliance in IPF patients lead to changes in trans-diaphragmatic gradient and in LES function thus favoring reflux? PPIs might be beneficial, even though the evidence about their efficacy is controversial. Further large randomized controlled trials are needed to confirm the preliminary data about safety and efficacy of laparoscopic anti-reflux surgery.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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