



A narrative review of minimally invasive fundoplication for gastroesophageal reflux disease and interstitial lung disease

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: N Tamburini; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Interstitial lung disease (ILD) encompasses a heterogeneous group of acute and chronic disorders characterized by diffuse pulmonary infiltrates with histologic features of pulmonary inflammation, dyspnea, and restrictive lung patterns. Gastroesophageal reflux disease (GERD) and ILD are two pathological conditions often strictly related, even if a clear relationship of causality has not been demonstrated. The mechanisms leading to ILD are not completely understood, although it is recognized that different factors are involved. In recent years, it has been suggested that acid gastroesophageal reflux is an important cause of both systemic sclerosis (SSc)-ILD and idiopathic pulmonary fibrosis (IPF). It has been hypothesized that micro aspiration of gastric material may play a fundamental role in the fibrotic transformation of pulmonary parenchyma. According to that, some studies have described antireflux procedures for patients affected by ILD and GERD. However, although some studies reported good results in terms of improvement of lung function, the role of antireflux surgery remains uncertain as well as not univocal. An extensive literature search was performed from January 1970 to 31 December 2020 in PubMed and the Cochrane Central Register of Controlled Trials. The research was limited to English-language studies. The aim of the present study was to summarize the effect of antireflux surgery for the treatment of abnormal acid GER on the natural history of this disease.

Keywords: Idiopathic pulmonary fibrosis (IPF); gastroesophageal reflux disease (GERD); fundoplication; interstitial lung disease (ILD); treatment; surgery

Received: 21 January 2021; Accepted: 23 March 2021; Published: 25 December 2022.

doi: [10.21037/aoe-21-7](https://doi.org/10.21037/aoe-21-7)

View this article at: <http://dx.doi.org/10.21037/aoe-21-7>

Introduction

Interstitial lung disease (ILD) is the nomenclature used to describe a heterogeneous group of pulmonary disorders characterized by extracellular infiltration of terminal bronchioles and acini causing interstitial-alveolar inflammation (1), leading to diffuse fibrosis, respiratory failure, and death (2). Patients suffering from these diseases

present with dyspnea, rales, finger clubbing, exercise induced hypoxemia, and typical interstitial radiographic changes. There is growing evidence of the association between gastroesophageal reflux disease (GERD) and some forms of ILDs, such as idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc) (3). Despite the different histopathology, IPF and SSc-ILD present some similarities, including clinical symptoms and the basal

subpleural distribution of fibrosis recognizable at the high-resolution computed tomography (HRCT). GERD has been considered to play an important role in development and progression of IPF through micro-aspirations of acid and non-acid refluxate (4,5). Indeed, several studies showed that laparoscopic fundoplication in patients with IPF slowed the progression of the disease, other than providing GERD control (6-8). Since esophageal motility is commonly affected by SSc, it is difficult to determine whether a causal connection between GERD and SSc-ILD exists. In addition, the role of antireflux surgery in these patients has been poorly defined.

The aim of this report was to review the current available evidence on the role of antireflux procedures in patients with ILDs. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://aoe.amegroups.com/article/view/10.21037/aoe-21-7/rc>).

Methods

A literature search of PubMed, SCOPUS, Cochrane Central Register of Controlled Trials, and Google Scholar databases was performed to include articles published between January 1970 and December 2020. The following key words were used: ‘interstitial lung disease’, ‘systemic sclerosis’, ‘GERD’, ‘antireflux surgery’, ‘pulmonary fibrosis’, ‘antireflux therapy’, ‘micro-aspiration’, ‘gastroesophageal reflux’, ‘scleroderma’, ‘Roux-en-Y’, ‘fundoplication’. The reference list of selected articles was also reviewed to identify additional relevant publications.

IPF

The prevalence reflux in patients with IPF varies extensively (12–94%) (9). Already in 1971, Pearson *et al.* (10) were looking at GERD as a possible underlying cause of unexplained pulmonary fibrosis. Of 143 patients with reflux and hiatal hernia, 6 (4%) presented respiratory symptoms and radiological signs consistent with IPF. Similarly, Mays *et al.* (11) found a higher incidence of hiatal hernia and GERD in patients with IPF compared to the age-matched controls. In a pH-monitoring study by Pellegrini *et al.*, the authors found for the first time a temporal correlation between episodes of reflux and respiratory symptoms, suggesting that repeated episodes of acid micro aspiration can contribute to the pathogenesis of chronic pulmonary inflammation (12). Nevertheless, the authors were unable to

prove that gastric refluxate reached to the upper esophagus and ultimately spilled into the tracheobronchial tree, because pH-monitoring assessed only the distal esophagus. In 1992, Patti *et al.* found that peristalsis of lower sphincter (LES), upper sphincter (UES), and esophageal body were significantly deficient in patients with respiratory symptoms of unknown origin (13). Thereafter, Tobin *et al.* Recorded the presence of GERD in 16 of 17 patients with IPF, but just 25% had symptomatic reflux (14). Numerous studies have shown that antireflux medications and interventions can relieve respiratory symptoms in most patients, however, despite the clinical evidence, the underlying physio pathological mechanisms are still not well understood (15,16). A chronic immune response self-sustained by inflammatory cytokines targeting the interstitium of terminal bronchi and alveoli could be triggered by the refluxate. Krishnan *et al.* (17) provided evidence of micro aspirations in symptomatic patients, by detecting high levels of tracheal pepsin in those with GERD. Accordingly, Davis *et al.* (18) found high levels of pepsin in the bronchoalveolar lavage fluid (BALF) of patients undergoing lung transplantation for various chronic lung diseases, including IPF. Finally, Savarino *et al.* (19) proved the direct association between gastric refluxate reaching the proximal esophagus and respiratory symptoms, and that these episodes happened more frequently in IPF patients, compared to non-IPF subjects with similar esophageal manometric profile.

Role of antireflux surgery

Pulmonary symptoms improvement after open fundoplication in patients with chronic aspiration was first described by Pellegrini *et al.* (12) (Table 1). Similar results with a laparoscopic approach were reported by Patti *et al.* (20) in the early 2000s. The authors found that 83% of patients with cough after reflux episodes detected with pH-monitoring, had resolution of their respiratory symptoms after laparoscopic antireflux surgery (LARS). Similarly, Ciofica *et al.* (21) reported a significant improvement of all respiratory symptoms and quality of life of 126 patients undergoing LARS. Furthermore, Cantu *et al.* performed a pulmonary functional assessment of patients after LARS, showing improved FEV1 and lower rates of bronchiolitis obliterans syndrome (BOS) (22). In 2006, Linden *et al.* (6) compared lung function of 14 end-stage IPF patients who underwent LARS with that of 31 IPF patients waiting for transplant who did not undergo fundoplication. Over a 15-month period, they observed a stationary lung function

Table 1 Antireflux surgery and IPF studies

| Author | Year | Type of study | Population size | Results |
|------------|------|---|-----------------|--|
| Pellegrini | 1979 | Retrospective cohort study | 5 | Raising of the lower esophageal pressure and normalization of the reflux status by 24-hour pH-monitoring standards |
| Patti | 2000 | Retrospective cohort study | 39 | Improvement of respiratory symptoms in 83% of cases when a temporal correlation between cough and reflux was found on pH-monitoring |
| Ciovica | 2005 | Retrospective cohort study | 126 | Significant improvement of both respiratory symptoms and quality of life |
| Linden | 2006 | Retrospective cohort study | 45 | No perioperative complications and no decrease in lung function over 15-month follow-up. Patients who underwent fundoplication had stable oxygen requirement compared to controls |
| Lee | 2011 | Retrospective cohort study | 204 | Prolonged median survival time (1,967 vs. 896 days) and lower radiologic fibrotic score (14% vs. 19%) for PPI/H2RA vs. controls |
| Fisichella | 2011 | Prospective study | 19 | lung transplant patients with GERD had more pepsin in their BALF than lung transplant patients who underwent LARS |
| Raghu | 2013 | Retrospective cohort study | 14 | FVC evaluated before and after LARS showed increase of mean FVC (+0.08 L) after surgery |
| Raghu | 2018 | Prospective randomized controlled study | 58 | LARS was associated with lower decline of FVC (−0.05 vs. −0.13 L), longer time to FVC decline or death, fewer clinical events and deaths. Most common adverse events after surgery were transient dysphagia and abdominal distention |

IPF, idiopathic pulmonary fibrosis; BALF, bronchoalveolar lavage fluid; GERD, gastroesophageal reflux disease; LARS, laparoscopic antireflux surgery; FVC, forced vital capacity.

of LARS patients compared to a substantial increase in oxygen requirements of those who did not received antireflux surgery. In multiple studies by Raghu *et al.*, IPF patients after laparoscopic fundoplication achieved stabilization of respiratory physiological function and oxygen requirements, with a 2-year survival rate of 81.5% (23-25). Another study detecting pepsin levels in BALF found lower amounts in transplant patients who did undergo LARS compared to those who did not. In addition, more rapid development to BOS and acute rejections were found in patients with higher pepsin levels (26). These results led Patti *et al.* to assess LARS effectiveness, concluding that the protective effect of fundoplication was due to the ability of minimizing GERD-related stress on chronic allograft injury (27). The WRAP-IPF trial was a multicenter, unblinded randomized clinical trial with patients randomized to either laparoscopic anti-reflux surgery or no surgery. In addition to DeMeester score decrease, the authors found a trend towards normalization of forced vital capacity (FVC) (28). Finally, Lee *et al.* (8) demonstrated that Nissen fundoplication was associated with a lower HRCT fibrosis score and revealed to be an independent predictor of IPF patients' survival (8). Unfortunately, the small sample

size of available studies does not allow to draw any definitive conclusion, and further study is warranted to confirm the impact of antireflux surgery on disease progression in this population.

SSc

Pulmonary disease is frequent in SSc (29) and the main cause of mortality in SSc is ILD (30). Although factors such as cellular and humoral immunity, genetic, environmental conditions are involved, the mechanisms leading to SSc-ILD are not well known (31,32). Esophageal involvement is common in patients with SSc, accounting for 50% to 90% of cases (33,34). Several studies have investigated the relationship between esophageal dysmotility, GERD, and lung involvement in SSc patients (35-38). However, because of the common esophageal involvement in SSc, it is still not defined whether GERD and ILD are causally related when present together, or whether they are merely two common symptoms of a systemic disease. Two small sample studies evaluated esophageal function and pulmonary function tests in SSc patient with GERD; no correlation was established between the degree of esophageal involvement

Table 2 Antireflux surgery and SSc studies

| Author | Year | Type of study | Population size | Results |
|----------|------|----------------------------|-----------------|---|
| Orringer | 1981 | Retrospective cohort study | 37 | 31% of patients with strictures required intermittent dilatations. 65% of patients undergoing Collis gastroplasty showed reflux symptoms improvement |
| Poirier | 1994 | Retrospective cohort study | 14 | Reflux symptoms were relieved in 71% of cases |
| Kent | 2007 | Retrospective cohort study | 23 | Lower incidence of post-operative dysphagia in the RYGBP group. GERD-HRQOL significantly lower in that group compared to fundoplication group |
| Mansour | 1988 | Retrospective cohort study | 12 | All patients who underwent an antireflux procedure had recurrence of esophagitis or stricture or both at an average of 4 years postoperatively |
| Watson | 2006 | Retrospective cohort study | 26 | Reflux symptoms were controlled in 79% of cases at 5 years after surgery |
| Yan | 2018 | Retrospective cohort study | 14 | All RYGB patients had symptom resolution or improvement, while only 50% of patients reported partial improvement in the fundoplication group |
| Goldberg | 2016 | Retrospective cohort study | 34 | 41% were asymptomatic and 56% had reduced symptoms. Persistent dysphagia was noted 11.7% of cases and was successfully treated with endoscopic dilation |

SSc, systemic sclerosis; GERD, gastroesophageal reflux disease; HRQOL, health-related quality of life; RYGB, Roux-en-Y gastric bypasses.

and pulmonary function tests (35,36). Another research highlighted the link between the severity of esophageal motor disorders and the presence of ILD. Compared to those with moderate or no esophageal motor impairment, SSc patients with severe esophageal motor impairment showed a marked decline of median DLCO measures and a higher probability of ILD evidence on CT images (37). Another research conducted by the same group found that 32.3% had erosive esophagitis and 6.8% of patients had Barrett's esophagus (38). Another study found that SSc-associated ILD patients had higher esophageal acid levels, more reflux and more episodes of reflux that reached the proximal esophagus. However, compared to those without ILD, patients with SSc-associated ILD did not show a stronger association with impaired esophageal motility patterns (19). On the other hand, other two studies demonstrated association esophageal dysmotility with reduced lung volumes (39,40).

Role of antireflux surgery

In patients with SSc, surgical treatment of GERD is challenging because surgeons face an aperistaltic esophagus, sometimes with peptic sequelae, low-pressure LES, and often delayed gastric emptying. Limited research on the best surgical treatment for patients with SSc and reflux has been published so far (Table 2). Different types of fundoplication have been described in this patient

group, in which the gastric fundus is wrapped around the intraabdominal esophagus to recreate or raise the LES. Heterogeneous findings were published in previous publications evaluating fundoplication as a treatment for esophageal disease in patients with SSc (41,42). Despite an improvement of reflux symptoms in 50–60% of cases, some authors found postoperative dysphagia up to 70% of cases (42,43). On the other hand, another study found that 40% of patients, in addition to 50% who had residual but improved reflux symptoms, were postoperatively symptom-free and only 12% complained recurrent dysphagia (44). Mansour and Malone analyzed the long-term effectiveness of fundoplication, finding that all patients undergoing fundoplication had recurrent esophagitis within an average time of 4 years after surgery (45). Conversely, reflux symptoms improvement in almost 80% of cases was seen in another similar paper (46). Roux-en-Y gastric bypass (RYGB) has recently emerged as a potential treatment option for acid reflux (47). This technique helps to separate the acid-producing parietal cells from the distal esophagus, as well as to distally divert the bile. Regarding GERD treatment in patients with SSC, there was only one study specifically comparing RYGB to fundoplication. Despite the limited number of patients analyzed, those undergoing RYGB had significantly better GERD health-related quality of life (GERD-HRQOL) scores with less dysphagia (43). Furthermore, another research also found that, in terms of GERD symptom improvement and esophagitis resolution,

RYGB is superior to fundoplication (48). However, as no paper has evaluated the role of antireflux surgery on the progression of SSC-associated ILD, no definitive conclusions can be drawn.

Conclusions

Evidences, unfortunately, are mostly of low quality, based on observational and retrospective studies. Latest studies do not seem to confirm a better patients' outcome when surgery is used in the management of IPF associated with GERD. Further large randomized controlled trials are needed to confirm the preliminary data. Regarding SSc, there are no data to support the use of surgery for the treatment of SSc-associated ILD.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Timothy M. Farrell and Geoffrey Kohn) for the series “Minimally Invasive Procedures for Gastroesophageal Reflux Disease” published in *Annals of Esophagus*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://aoe.amegroups.com/article/view/10.21037/aoe-21-7/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://aoe.amegroups.com/article/view/10.21037/aoe-21-7/coif>). The series “Minimally Invasive Procedures for Gastroesophageal Reflux Disease” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoe-21-7

Cite this article as: Tamburini N, Andolfi C, Fisichella PM. A narrative review of minimally invasive fundoplication for gastroesophageal reflux disease and interstitial lung disease. *Ann Esophagus* 2022;5:42.