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BRN Rev. 2023;9(3):152-9

BRN Reviews

REVIEW ARTICLE

Gastroesophageal Reflux in Lung Transplantation

Sheila Izquierdo-Cuervo, MD, Sandra Tello-Mena, MD, and Víctor M. Mora-Cuesta, PhD*

Respiratory Department, Lung Transplant Unit, Marqués de Valdecilla University Hospital, ERN-LUNG (European Reference Network on Rare Respiratory Diseases), Santander, Spain

ABSTRACT

Gastroesophageal reflux disease (GERD) in lung transplant recipients has been associated with chronic lung allograft dysfunction (CLAD). CLAD is a leading cause of mortality in lung transplant recipients, and it is probably the result of a variety of immune, infectious, and inflammatory injuries.

GERD may contribute to CLAD since it is associated with a higher risk for post-transplant aspiration. Aspiration induces an inflammatory cascade in the lung allograft, thereby causing acute rejection. Recurrent episodes of acute rejection and allograft injury may then contribute to chronic rejection, resulting in graft failure. Poorer outcomes after transplantation, including early allograft injury, early rehospitalization, and chronic rejection are potentially modifiable risk factors for post-transplant mortality.

In patients with GERD, antireflux surgery may help preserve post-transplant lung function, improve immune response, and reduce the incidence of bronchiolitis obliterans syndrome and mortality. Early fundoplication improves survival and reduces the incidence of CLAD in lung transplant recipients.

Keywords: Antireflux surgery. Chronic lung allograft dysfunction. Fundoplication. Gastroesophageal reflux disease. Lung transplantation.

***Correspondence to:**
Víctor M. Mora-Cuesta
Email: victormanuel.mora@scsalud.es

Received: 15-07-2023
Accepted: 21-08-2023
DOI: 10.23866/BRNRev:2023-M0093
www.brnreviews.com

INTRODUCTION

Lung transplantation (LT) has been demonstrated to improve the quality of life and survival of patients with advanced pulmonary disease. Although lung transplant outcomes have improved over time, chronic lung allograft dysfunction (CLAD) continues to be the primary cause of morbimortality from the first year post-transplant.

CLAD is a complex multifactorial syndrome induced by allo- and autoimmune responses and exposure to external agents. Gastroesophageal reflux disease (GERD) is a highly prevalent, albeit modifiable, risk factor. Therefore, early diagnosis and treatment will improve long-term CLAD outcomes and survival.

Nowadays, there is enough scientific evidence about the negative effects of GERD on lung allograft post-transplant. Additionally, early management of GERD has been proven to reduce the risk for CLAD. However, consensus has not yet been reached with respect to the optimal diagnostic and therapeutic approach to GERD in candidates for LT and LT recipients.

IMPLICATIONS

As many as 30 to 65% of LT candidates suffer from GERD[1]. This disease is most commonly found in patients with diffuse interstitial lung disease and cystic fibrosis. Following transplantation, the prevalence of GERD may double, being higher in patients undergoing double LT and re-transplantation.

The diagnosis of GERD is simple and intuitive, as it is based on the onset of local symptoms or complications in the esophageal mucosa, secondary to the reflux of gastroduodenal contents into the esophagus. GERD, however, is a complex disease difficult to evaluate in LT, since it is influenced by multiple factors related to the surgical technique and drug therapy administered. One of these factors is damage to the vagus nerve during surgery. Other factors include deterioration of mucociliary clearance and cough resulting from allograft denervation, along with the adverse effects of immunosuppressive therapy. Other risk factors are gastroparesis caused by postoperative neuropathy and analgesic and immunosuppressive treatments, disruption of the antireflux barrier secondary to the presence of a hiatal hernia or phrenic paralysis, changes in thoracoabdominal pressure resulting from postoperative changes, and changes in respiratory mechanics. Other associated factors include laryngopharyngeal dysfunction related to long-term orotracheal intubation, potential damage to the recurrent laryngeal nerve, critical-illness myopathy and dysmotility, or absence of esophageal motility[2].

Although the association between gastroesophageal reflux (GER) and CLAD is widely known, the underlying mechanism of this association is not fully understood. The most widely accepted hypothesis is that silent, recurrent, acid and non-acid microaspirations of gastroduodenal contents into the lung allograft would cause direct chemical damage, impair innate immunity, and promote the pro-inflammatory cytokine storm. As a result, allograft lung injury and inflammation occur, followed by the formation of a scar that ultimately causes irreversible CLAD. The most

prevalent CLAD subtype is bronchiolitis obliterans syndrome (BOS), which is very frequently studied in GER[2,3].

Different approaches have been adopted to explore GER in LT recipients. Some studies have demonstrated that esophageal multichannel intraluminal impedance and pH testing may be valuable in detecting GER and establishing its association with early allograft injury[4]. A similar study based on the same technique revealed that pre-transplant GERD, defined as increased acid exposure, was associated with a shorter time free to BOS following transplantation[5].

On another note, there is evidence that the aspiration of gastroduodenal contents generates a pro-inflammatory and profibrotic environment within the lung allograft and impairs defense systems such as alveolar macrophages and surfactant lipids[6]. A range of studies have been conducted to identify potential markers of aspiration, including the presence of conjugate bile acids, such as taurocholic acid, and inflammatory proteins in bronchoalveolar lavage at three months post-transplant[7]. There is evidence that the presence of conjugate acids in bronchial aspirate is predictive of bacterial infection, CLAD, and mortality[8,9].

Another recent study revealed that pre-transplant GERD is associated with the presence of autoantibodies, including anti-collagen type V and anti-K-alpha1 tubulin antibodies. This association is probably due to exposure of these molecules to inflammatory response secondary to GER[10]. The presence of these anti-collagen type V and anti-K-alpha1 tubulin antibodies has been associated with the development of CLAD post-transplant[11].

Pepsin has also been widely studied. The presence of elevated concentrations of pepsin in bronchoalveolar lavage has been related to more frequent and severe episodes of acute cellular rejection and more rapid progression to BOS[12].

DIAGNOSIS

The goal of diagnosis is to ensure early identification of patients at a higher risk of developing chronic lung allograft injury secondary to GER and, therefore, having poor transplant outcomes. A standard protocol has not yet been established to determine the type and timing of studies. According to the literature, traditional symptoms such as pyrosis and regurgitation have a low predictive value for the presence of reflux in this population, as most patients remain asymptomatic. Non-acid reflux plays an essential role in post-transplant studies. Adopting a multidisciplinary approach to esophageal dysfunction is crucial since lung allograft injury is not only induced by the presence of esophageal reflux.

The scientific evidence available consistently demonstrates that the optimal timing for diagnosis is the early post-transplant period. During this period, lung allograft injury is still in an early phase and measures can still be adopted to prevent the progression of lung lesions. However, in this early phase, the pulmonary disease of the patient may hinder studies and interfere with results. Pre-transplant GERD may exacerbate as a result of the surgical procedure and treatment for LT.

Diagnostic studies that should be considered:

– Esophageal pH testing is the gold standard diagnostic technique in GERD. The most

important factors are acid exposure time (pH < 4), number of episodes of reflux, and DeMeester index. In contrast, esophageal multichannel intraluminal impedance and pH testing are the most widely accepted diagnostic techniques in LT. The reason is that this combined study provides more information and includes an examination of proximal reflux (closely related to microaspirations), non-acid reflux and bolus clearance, which have been associated with CLAD[4]. The American College of Gastroenterology recommends discontinuing treatment with proton-pump inhibitors at least seven days prior to pH testing.

– High-resolution esophageal manometry, when used as a complementary study, may provide useful information, since there are no manometric abnormalities that are specific to GERD. This study may be useful for inserting the catheter for the pH test, considering endoscopic versus surgical treatment of GER, and establishing a diagnosis of esophageal dysmotility. In this sense, the Chicago classification is very useful and has been used to obtain a standard clinical interpretation of the study. Esophageal dysmotility in LT has gained increased attention from the scientific community. This complication has an impact on GERD and allograft dysfunction, especially in the hypercontractile esophagus, which is the most frequent motility disorder in LT. This disorder is characterized by prolonged bolus clearance, thereby increasing the risk for microaspirations, which are closely related to early acute rejection and a lower forced expiratory volume in one second (FEV_1) post-transplant[13].

– Upper gastrointestinal endoscopy is useful for evaluating lesions in the esophageal mucosa, as a GER complication. Erosive esophagitis, especially in advanced stages (Los Angeles C and D), and Barret's esophagus are specific findings of GERD. The American College of Gastroenterology recommends discontinuing treatment with proton-pump inhibitors at least two to four weeks prior to the gastroscopy.

– Barium gastroduodenal esophageal transit is useful to evaluate anatomical abnormalities, stenoses, membranes, and hiatal hernia, among other disorders. The diagnostic value of GERD, however, is limited owing to the short duration of the study, and the variability and intensity of provocation maneuvers[14,15].

The studies described above identify GER. However, LT requires the use of methods for screening for aspiration, since it is the factor that induces allograft dysfunction. For such purpose, some biomarkers of aspiration are analyzed in bronchial samples. Thus, conjugated bile acids are analyzed by mass spectrometry, whereas pepsin is analyzed using the ELISA technique. These biomarkers are more representative in bronchial aspirate specimens than in bronchoalveolar lavage since the trachea and main bronchi are more proximal to the gastrointestinal tract[8,9]. Oil Red O staining with determination of lipid-laden macrophage index has also been used to detect alveolar foam cells and estimate the risk for pulmonary aspiration, respectively. This combined technique apparently has a poorer diagnostic value, as compared to histological analysis of aspiration by transbronchial biopsy[16].

Delayed gastric emptying or gastroparesis has a prevalence in lung transplantation as high as 23-91%[17]. In addition, this disorder is involved in allograft dysfunction, as it predisposes the patient to GER. Also, it augments the risk for microaspirations, as gastric content retention exacerbates esophageal reflux. The diagnostic technique of choice is gastric emptying scintigraphy, a nuclear medicine test that defines gastroparesis as a retention ≥ 10% of the radiotracer in gastric contents. This disorder is increasingly used in transplant surgery. However, it has been demonstrated to exert deleterious effects on LT recipients, as it is associated with acute cellular rejection and CLAD[17,18].

TREATMENT

Pharmacological treatment

The most widely used pharmacological treatments for gastroesophageal reflux are proton-pump inhibitors (PPIs), followed by histamine H2-receptor antagonists. These therapies are used to inhibit or reduce gastric acid, thereby reducing associated symptoms. These therapies do not exert any effect on the mechanism of esophageal reflux or on gastroduodenal content aspiration, which will ultimately cause lung injury. Therefore, these treatments may be effective in improving symptoms, rather than lung transplant outcomes.

Each transplant center has its own protocol for the use of PPIs. Some centers routinely use PPIs, whereas PPIs are used in other centers as a function of the presence of GER on the pH test or the occurrence of typical GERD symptoms.

Another less common pharmacological therapy is prokinetic agents, which facilitate bolus clearance at the esophageal and gastric level. However, the mechanism of reflux persists.

Surgical treatment

Although the management of GERD is based on the use of antisecretory agents, these do not influence esophageal dysmotility and do not prevent reflux or retrograde aspiration. Therefore, surgery may be required.

Several prospective, randomized, multicentric trials involving non-transplant patients reveal that laparoscopic antireflux surgery is superior to medical treatment in reducing symptoms, improving quality of life, and controlling gastroesophageal reflux.

Laparoscopic antireflux surgery is a widely validated method for the treatment of GERD and bronchial aspiration of gastrointestinal contents. It is a definitive treatment, since it is the only therapy that exerts direct effects on reflux. This treatment corrects aspiration into the lungs, in the absence of other risk factors such as esophageal dysmotility, anatomic esophageal-gastric barrier abnormalities and gastroparesis. In these cases, an individualized approach should be adopted.

Indications for the surgical management of GERD post-transplant include:

- evidence of symptomatic reflux;
- documented severe reflux on 24-hour pH test;

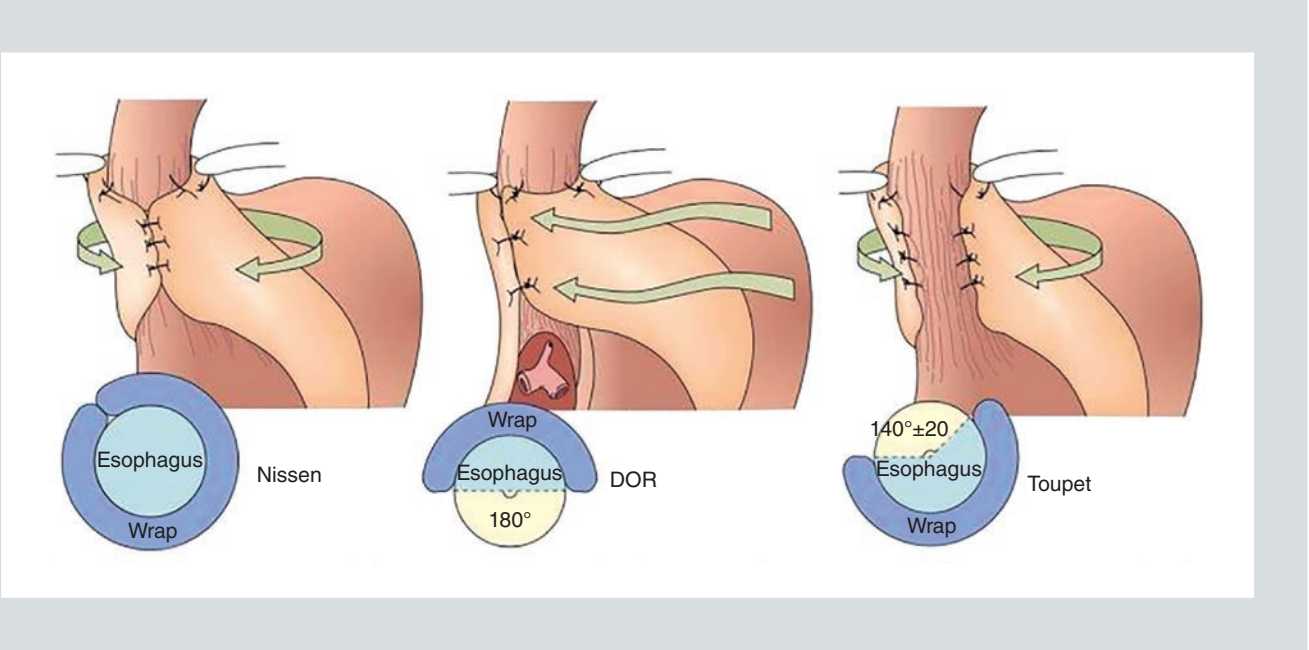

Figure 1. Three types of techniques *(adapted from Fieldman et al., 2021)*[19].

– documented reflux on impedancemetry and/or endoscopy (data consistent with esophagitis);

– evidence of aspiration on bronchoscopy;

– unexplained impairment of lung function[20].

Anti-reflux surgery involves reducing hiatal hernia, reconstructing the diaphragmatic hiatus and increasing pressure of the lower esophageal sphincter. The technique is currently performed by laparoscopy. Based on the level of fundoplication, there are three types of techniques (Figure 1).

The type of fundoplication is established based on the patient's history of surgical procedures, manometry studies, symptoms of dysphagia or underlying diagnosis of the lung recipient. The most common techniques are Nissen and Toupet. Nissen corrects GER more effectively in the long term but is associated with a longer incidence of postoperative dysphagia and difficulty passing gas. Toupet is more frequently used in cases of reduced esophageal motility, due to its lower associated incidence of dysphagia.

The optimal timing for the intervention is as early as possible to prevent the deleterious effects of GER on the lung allograft. However, it is necessary to wait until the lung recipient has recovered sufficient functional status to be able to undergo this type of surgery.

RESULTS

Anti-reflux surgery has been proven to be effective in reducing levels of bile acids and pro-inflammatory cytokines in the airways. It is still unknown whether bile acids are direct effectors of lung injury, pro-inflammatory agents that promote alloimmune damage, markers of aspirate, or a combination of all[21].

Fundoplication following lung transplant has been demonstrated to prevent CLAD. It is associated with reduced mortality, especially when performed in the early post-transplant period (within three-six months post-transplant). In addition, this technique reduces or improves the general rate of lung function deterioration, especially when performed before the onset of CLAD. These effects are explained by the fact that GERD correction surgery improves the pro-inflammatory and fibrogenic environment induced by aspiration[20,22-24].

SAFETY

Laparoscopic antireflux surgery is associated with minimal perioperative morbidity and shorter hospital stays in non-recipients. Lung transplant recipients show similar morbidity rates, but a longer length of hospital stay probably owing to the need to readjust immunosuppressive treatments[25].

Low mortality rates (1.4%) have been reported in relation to anti-reflux surgery[26]. Nevertheless, postoperative complications may arise, including delayed gastric emptying requiring endoscopic dilatation or botulin toxin injection; dysphagia, nausea, unremitting vomiting, and bleeding, among others. These complications are similar to those documented in patients undergoing other types of surgical procedures. Therefore, fundoplication may be considered a safe, effective treatment following lung transplantation[25,26].

CONCLUSIONS

In accordance with the literature, early screening for GERD is recommended in all lung transplant recipients, regardless of the symptoms they may develop. An analysis of the aspirate is also recommended, in light of the role that this complication plays in the development of chronic lung allograft dysfunction.

In the case of GERD, early, multidisciplinary, definitive management is recommended. Thus, treatment should involve antireflux surgery to delay lung function impairment and improve long-term survival in lung transplant recipients. Further multicentric, prospective, protocolized studies are needed to obtain conclusive evidence of the optimal diagnostic and therapeutic approach to this disease.

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