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Review

Airway Complications after Lung Transplantation

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Abstract

Lung transplantation in patients with end stage lung disease can improve survival and quality of life. Airway complication incidence varies between 2-33%, but the true incidence is difficult to determine due to a lack of validated classification systems. There are many risk factors for post lung transplant airway complications, the most common being anastomotic ischemia, pulmonary infections, surgical technique and allograph dysfunction. Common complications include formation of granulation tissue, anastomotic stenosis, bronchial fistulas, anastomotic dehiscence, transplant related bronchomalacia and anastomotic infections. While the incidence of airway complications post-transplantation is low, they are associated with significant morbidity. Most of the complications can be managed via bronchoscopic interventions, but do require repeated procedures and hospitalizations.

Keywords

Lung transplantation; airway complication; granulation; anastomotic stenosis; anastomotic dehiscence; anastomotic infections; bronchial fistula; tracheobronchomalacia

1. Introduction

Lung transplantation in patients with end stage lung disease can improve survival and quality of life [1, 2]. Survival rates of lung transplantation have continued to improve, but the median length of survival remains only between 6-7 years [3, 4]. Various complications can occur after lung transplantation. Airway complications are associated with significant morbidity and mortality [5, 6]. Airway complications are also associated with increased hospitalizations, healthcare resource utilization, significant functional impairment and poor quality of life [7, 8].

Airway complication incidence varies between 2-33% [5, 9-11] but the true incidence is difficult to determine due to a lack of validated classification systems. While no gold standard currently exists, the ISHLT has proposed one [12]. Currently, classification of airway complications can be done based on the severity of airway necrosis [13] or based on variable degrees of anastomotic healing [5]. Common complications include formation of granulation tissue, anastomotic stenosis, bronchial fistulas, anastomotic dehiscence, transplant related bronchomalacia and anastomotic infections.

Multiple pathways have been described to clarify the factors that lead to airway complications. Postoperative ischemia due to disruption of arterial supply during lung harvesting and dependency on retrograde flow pressure while collaterals develop can lead to poor healing [14, 15]. Primary graft dysfunction, acute rejection, donor recipient height mismatch, prolonged mechanical ventilation, use of sirolimus in the early post-transplant period, and colonization with aspergillus fumigatus have also been associated with development of airway complications [9, 16-18]. Many of these revolve around airway ischemia, such as acute cellular rejection being associated with reduced perfusion of the donor airway as assessed by doppler blood flow in the donor airway submucosa. Management of these conditions vary between physicians and institutions with very few randomized controlled trials available to help guide therapy. In this review, we describe airway complications commonly associated with lung transplantations and their management.

2. Risk Factors

There are many risk factors for post lung transplant airway complications, the most common being anastomotic ischemia, pulmonary infections, surgical technique and allograph dysfunction. Both the pulmonary and bronchial circulation normally perfuse the airway and lungs. After lung transplantation, only the pulmonary circulation is usually reestablished. It takes approximately 2-4 weeks for collaterals to develop and in this time period, the lungs have to rely only on a single blood supply therefore increasing the risk of ischemia [19-23]. This ischemia leads to an inflammatory cascade that can cause remodeling of the bronchial lumen and airway dysfunction. Bronchial artery revascularization (BAR) during lung transplantation may be a viable technique to minimize early anastomotic complications [24]. BAR is a complex procedure with potential risk or increased graft ischemic time and is therefore not routinely performed.

The length of the donor bronchus also affects the degree of airway ischemia. A shorter donor bronchus requires a shorter distance for collaterals develop and therefore reduces ischemic time. The incidence of airway complications in the first year after lung transplantation has been shown to decrease when the bronchus is shortened at the lobar carina [25]. Surgical techniques also play a part in predisposing patients to airway complications. End-to-end anastomotic technique without tissue overlap, also known as telescoping, is preferred and has a lower rate of airway complications.

[26] Telescoping technique has a 48% incidence of airway complications. While less commonly performed, the telescoping technique is sometimes necessary in patients with a significant difference in diameter of the donor and recipient bronchus. Sture technique is a common concern regarding possible post-transplant complications. Of the 740 patients, 462 received the continuous suturing technique and 278 received the interrupted suturing technique. Most demographic and clinical data were not statistically significant between the two groups, and those that were significant were not associated with worse survival outcomes, with the exception of the variable diagnosis. Bronchial complications were comparable between the continuous and interrupted groups (12.6% versus 10.4%, P = 0.382) [27]. Furthermore, wrapping the anastomosis in omental flaps, pericardial fat pads, arterial pedicles, and muscle flaps, all were tried in an attempt to improve donor tissue ischemia and did not result in any improvement in outcomes [12]. In addition to procedural consideration, immunosuppressive risk factors are relevant. The use of sirolimus, a rapamycin derivate, has also been associated with a high incidence of dehiscence if used early in the post-operative period [28]. The use of sirolimus, a rapamycin derivate, has also been associated with a high incidence of dehiscence if used early in the post-operative period. Finally, mechanical ventilation is an important component in the perioperative management of lung transplant. Mechanical ventilation poses a risk of bronchial ischemia, as it damages the bronchial mucosa and increases arterial resistance [29]. Other risk factors are listed in Table 1 and include suturing technique, short telomeres, BMI, time on ventilator and need for extracorporeal membrane oxygenation (ECMO), choice of induction medications, pulmonary infections and finally allograph dysfunction [9, 18, 25, 27, 28, 30-33]. There is no increase in risk of airway complications with idiopathic pulmonary fibrosis by itself though [34].

Table 1 Risk factors for airway complications.

Intermittent sutures	Theoretical risk over continuous sutures
Short telomeres	Higher risk of dehiscence and stenosis
BMI > 25 kg/m^2	Increased risk of complications - HR 2.48
Donor time on the ventilator prior to organ recovery	Highest probability when donors on mechanical ventilation for 50-70 hours prior to recovery
ECMO	Post transplant - HR 2.8
Baisiliximab induction	Dehiscence in ~4.8%
Sirolimus	Associated with issues with wound healing and high rates of airway complications
Pulmonary Infections	Preoperative infection with Burkholderia Cepacia and post operative infection by aspergillus fumigatus

3. Airway Complications

Airway complications are divided into both anastomotic complications and non-anastomotic complications. Anastomotic conditions include dehiscence, granulation tissue formation, anastomotic infection, airway stenosis, and fistula formation, while bronchial complications include post transplantation bronchomalacia and non-anastomotic infections. When these complications

are identified, regular repeat bronchoscopies and imaging should be utilized to assess appropriate healing of airway complications [25, 35].

4. Anastomotic Stenosis

Anastomotic stenosis is the most common airway complication following lung transplantation and can be seen in up to 40% of patients [36] (Figure 1). While it can develop at any point after transplantation, it is most commonly seen in the first 2-9 months [37, 38]. The development of an anastomotic stenosis is an independent risk factor for death after transplantation [28]. Risk factors for anastomotic stenosis are ischemia, severe reperfusion edema and early rejection. Stenosis can be classified as central airway strictures when they are within 1 cm of the suture line and non-anastomotic airway strictures when they are distal to the anastomotic stoma or lobar bronchus. Airway stricture occurring in bronchial or segmental airways is also called vanishing airway syndrome. Vanishing airway syndrome is associated with significant mortality with a mean survival of only 25 months [12].

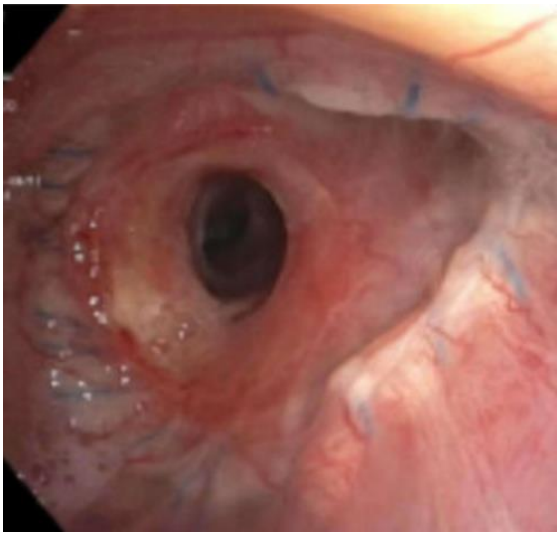

Figure 1 Anastomotic stenosis in the right mainstem bronchus.

Early post-transplant bronchial stenosis has an incidence of about 13% [11] and is due to ischemia, edema, necrosis of the mucosa. Late stenosis is seen in 2.5-3% [12] and is mainly due to fibrosis or bronchomalacia due to ischemia, rejection or infections [39]. Management is complicated and can involve multiple and repeated procedures.

The initial treatment of bronchial stenosis involves balloon bronchoplasty which is performed using controlled radial expansion balloons. Radial incisions at the site of the stenosis may also be peformed using cutting balloons or electrocautery which may improve long term resolution of a web like stenosis. Stent placement can be considered in patients refractory to balloon dilation with the goal to restore near physiologic airway patency. (Figure 2) The presence of a stent can lead to endobronchial remodeling over time therefore resolving the stenosis, but may also develop airway malacia after stent removal. Patients with stent placement demonstrate an improved mean survival as compared to the use of bronchoplasty alone [36]. Stents also have the advantage of being available in multiple sizes and can be placed via flexible bronchoscopy. Multiple types of stents can be used with novel stents now available. Small pilot studies shows that biodegradable stents are a

safe, effective and reliable alternative to classical metallic stents in patients with anastomotic stenosis after lung transplantation, and may avoid the need for permanent stenting [40]. These novel stents, while promising for future use, still require study on a large scale. Regardless of the stent type however, the complications from stents are similar [41]. Silicone stents however can be easily removed without scar tissue formation.

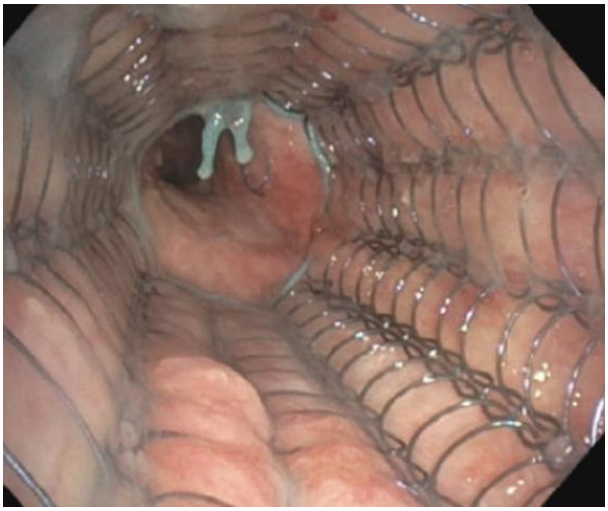

Figure 2 Right mainstem metallic uncovered self-expanding stent for anastomotic stenosis.

Other available techniques include cryoablation, laser photoresection, electrocautery and airway brachytherapy. Cold therapies such as cryotherapy and cryospray are preferred over thermal therapies due to the reduced risk of inflammation and subsequent granuloma formation [42]. Topical mitomycin-c [43] or submucosal injection of steroids have also been used with indication that it may delay restenosis, but no controlled trials are available. When balloon dilation and stenting fails, retransplantation, wedge bronchoplasty or isolated sleeve reduction of the bronchus intermedius or lobectomy can be considered.

5. Anastomotic Dehiscence

Dehiscence is usually due to airway necrosis and is an early complication commonly occurring within five weeks of transplantation. Incidence has been reported anywhere between 1-10% of patients [44] and is associated with a high mortality rate. Risk factors include high-dose steroid use in the perioperative period, immunosuppression, fungal infection, and acute rejection [18]. Clinically significant dehiscence is seen in only about 2% of patients. Bronchoscopy is the gold standard for diagnosis of anastomotic dehiscence, but computed tomography of the chest can help detect defects at the anastomotic site and can show bronchial narrowing or extraluminal air. When necrosis only involves the bronchial mucosa and not the entirety of the bronchial wall and no air leak is present, conservative management with antibiotics and surveillance bronchoscopy may be done [45]. An uncovered self-expanding metallic stent may be deployed when clinically significant anastomotic dehiscence is present to facilitate healing [44, 46]. Uncovered metallic stents tend to initiate granulation tissue formation and can help with epithelialization and healing of the defect. For larger defects seen in dehiscence, a covered metallic stent can also be utilized. Platelet rich

plasma may be used in small dehiscence to promote healing via the increase of growth factors, collagen and fibroblasts [47]. When conservative measures fail or in patients with severe dehiscence, reanastomosis, and flap bronchoplasty. Retransplantation can also be considered when alternative approaches are not viable. Surgical approaches however may not yield the best long-term outcomes.

6. Granulation Tissue

Granulation tissue formation is common and up to 20% of patients will develop obstructive granulation tissue within months of lung transplantation [48] (Figure 3). Aspergillus infection at the surgical site is a common risk factor for development of excessive granulation tissue [49]. Granulation tissue can lead to a fixed intrathoracic obstruction, reduce lung function, and can also lead to post-obstructive pneumonia. Management differs based on the degree of obstruction due to granulation tissue. Mechanical debridement via flexible or rigid forceps is very effective in removing non-obstructive granulation tissue formation. Alternatives such as laser therapy, electrocautery, radiofrequency ablation, argon plasma coagulation and cryoablation [50] can also be used, but tend to cause more trauma and can lead to further inflammation and possibly the development of additional granulation tissue. More extensive debridement is required when granulation tissue leads to obstruction. All the interventions mentioned above may be used, but cryodebridement may be effective in debulking tissue without causing more inflammation.

Figure 3 Granulation tissue narrowing surgical anastomosis.

7. Bronchial Fistulae

Bronchial fistulas may be bronchopleural, bronchomediastinal, or bronchovascular. Prolonged bronchial ischemia can lead to necrosis and development of these types of fistulas [51]. Patients with bronchopleural fistulas can present with shortness of breath, hypotension, subcutaneous emphysema, and pneumothorax and is initially managed with tube thoracostomy if pneumothorax is present. Broad spectrum antibiotic and antifungals are also initiated. Bronchopleural fistulas can be managed either surgically or bronchoscopically. Surgical interventions include open drainage, direct closure with flap, thoracoplasty, or transsternal bronchial closure [52]. Fibrin glue may be applied bronchoscopically in small defects while metallic stents are used for larger, more proximal

fistulae. The use of metallic stents promotes granulation formation and can help seal the fistula site. Devices such as the Amplatzer device can also be used in select cases [53]. When bronchomediastinal fistulas are present, patients will present with signs and symptoms of mediastinal infections. Aerosolized antibiotics are the standard of care, but in severe infections, mediastinal debridement may be necessary. Bronchovascular fistulas are associated with significant morbidity. Fistulas may be formed between the bronchus and the aorta, pulmonary artery, pulmonary vein or left atrium. Patients present with hemoptysis and can progress to massive hemorrhage. Emergent bilobectomy or pneumonectomy may be successful in some cases, but most interventions have a low likelihood of success [52, 54]. Finally, retransplantation can be considered if above techniques fail.

8. Post Transplant Tracheobronchomalacia

Post-transplant, tracheobronchomalacia is the excessive bowing of the posterior tracheal or bronchial membrane during expiration (Figure 4). While some amount of bowing is normal, significant malacia is defined as a greater than 50% reduction in the lumen caliber on expiration [55]. After transplant, bronchomalacia may be perianastomotic (within 1 cm of the anastomosis site) or diffuse [12]. The incidence of post-transplant malacia is up to 4% based on single center studies [56]. Patients may present with dyspnea, barking cough, and recurrent respiratory infections. Spirometry can show declining flow rates and abnormal flow-volume patterns showing variable obstruction, more in expiration. While the cause is not clearly understood, bronchiolitis obliterans (BOS) has been associated with this condition [57]. Diagnosis requires direct visualization of the airway during dynamic airway maneuvers. Management is similar to that of tracheobronchomalacia in non-transplant recipients. When minimal clinical symptoms are present, aggressive pulmonary hygiene and use of continuous positive airway pressure (CPAP) ventilation during sleep is beneficial. Severe malacia may benefit from stent placement which can be temporary if airway remodeling occurs, but may need to be permanent. Surgical options include resection, reconstruction, tracheoplasty and retransplantation, but are rarely used [58, 59].

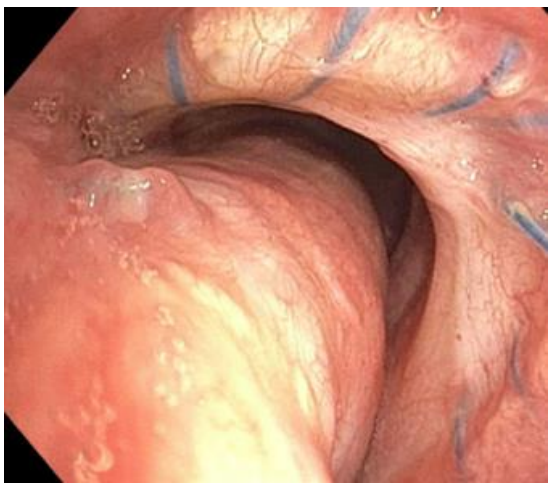

Figure 4 Severe malacia of the left sided anastomosis.

9. Anastomotic Infections

Fungal infections, especially by *aspergillus fumigatus*, at the anastomotic site can be serious. Patients with transplanted lungs have environmental exposures in the setting of significant immunosuppression. In the post-transplant period, there is disruption of lymphatics, alteration in mucociliary function and alveolar phagocytic function at the anastomotic site leading to increased risk of fungal infections [60]. Patients with anastomotic infections can be asymptomatic, but can also have fevers, cough, hemoptysis, wheezing and change in spirometry. Fungal infections by aspergillus and candida account for up to 35% of infections in lung transplant recipients [61]. Additionally, these patients are also at a higher risk for bacterial infections. It is therefore very difficult to determine if bacteria or fungi isolated after bronchoscopy are colonizers/commensals or are causing infection at the anastomotic site or elsewhere in the transplanted lung. Brushings and biopsies from the anastomotic site are the test of choice for the diagnosis of purely anastomotic infections. Antifungal prophylaxis is very important in preventing fungal infections. Prompt treatment for bacterial causes should also be initiated in these cases.

10. Conclusion

While the incidence of airway complications post-transplantation is low, they are associated with significant morbidity. Most of the complications can be managed via bronchoscopic interventions, but do require repeated procedures and hospitalizations. Surgical interventions are sometimes needed as is repeat transplantation. While literature on management of these complications continues to grow, expert opinion and physician preference is still the current cornerstone of management. Further research is necessary to better understand the outcomes of various interventions and to determine the best therapies for these conditions.

Author Contributions

Syed Mahmood and Amit Mahajan contributed equally in the conception, research, writing and editing of this manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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