



Airway complications in lung transplantation

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Abstract: Airway complications (ACs) after lung transplantation remain an important source of morbidity and mortality despite significant advances in the surgical techniques, leading to increased cost, and decrease quality of life. The incidences of ACs after lung transplantation range from 2% to 33%, even though most transplant centers have reported rates in the range of 7% to 8%. However, the reported rate of ACs has been inconsistent as a result of a lack of standardized airway definitions and grading protocols before the recent 2018 International Society for Heart and Lung Transplantation (ISHLT) proposed consensus guidelines on ACs after lung transplantation. The ACs include stenosis, perioperative and postoperative bronchial infections, bronchial necrosis and dehiscence, excess granulation tissue, and tracheobronchomalacia (TBM). Anastomosis infection, necrosis, or dehiscence typically develops within the first month after lung transplantation. The most frequent AC after lung transplantation is bronchial stenosis. Several risk factors have been proposed to the development of ACs after lung transplantation, including surgical anastomosis techniques, hypoperfusion, infections, donor and recipient factors, immunosuppression agents, and organ preservation. ACs might be prevented by early recognition of the airway pathology, using advance medical management, and interventional bronchoscopy procedures. Balloon bronchoplasty, cryotherapy, laser photo resection, electrocautery, high-dose endobronchial brachytherapy, and bronchial stents placement are the most frequent interventional bronchoscopic procedures utilized for the management of ACs.

Keywords: Lung transplantation; airway complications (ACs); airway ischemia reperfusion and grading; anastomosis dehiscence; bronchial stenosis; endobronchial infections; bronchial balloon dilation; bronchial stent placement; risk factors

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Introduction

In the early years after it was performed the first lung transplant in 1963 by Dr. James Hardy, bronchial complications, mainly necrosis, and dehiscence were the most frequent cause of morbidity and mortality in those patients who survived the first two post-operative weeks (1). Despite the high early incidence of airway complications (ACs), the recent advances made in organ preservation, surgical techniques, and the medical management of the recipient have contributed to a significant decreased in the ACs rates from as high as 80% to 15% (1-4). The reported incidence of ACs after lung transplantation has been inconsistent as a result of a lack of standardized

definitions and grading protocols before the recent 2018 International Society for Heart and Lung Transplantation (ISHLT) proposed consensus guidelines on ACs after lung transplantation (5), which has been accepted as a universal airway grading by the lung transplant society. Contrary to the previous classification protocols, the ISHLT system grades the severity, location, and extent of each type of ACs including, ischemia, necrosis, dehiscence, stenosis, and malacia (*Table 1*). The ISHLT consensus also emphasized the importance of recognizing other airway pathologies, e.g., endobronchial fungal infections and endobronchial post-transplant lymphoproliferative disorder (PTLD), which can manifest as airway necrosis or stricture.

The management of ACs varies depending on the

Table 1 ISHLT adult and pediatric grading system for airway complications after lung transplant

Ischemia and necrosis (I)

Location

- (I) Perianastomotic-within <1 cm
- (II) Extending >1 cm from anastomosis to major airways (bronchus intermedius and distal left mainstem)
- (III) Extending >1 cm from anastomosis into lobar or segmental airways

Extent

- (I) <50% circumferential ischemia
- (II) >50–100% circumferential ischemia
- (III) <50% circumferential necrosis
- (IV) >50–100% circumferential necrosis

Dehiscence (D)

Location

- (I) Cartilaginous
- (II) Membranous
- (III) Both

Extent

- (I) 0–25% of circumference
- (II) >25–50% of circumference
- (III) >50–75% of circumference
- (IV) >75% of circumference

Stenosis (S)

Location

- (I) Anastomotic
- (II) Anastomotic plus lobar/segmental
- (III) Lobar/segmental only

Extent

- (I) 0–25% reduction in cross-sectional area
- (II) >25–50% reduction in cross-sectional area
- (III) >50% but <100% reduction in cross-sectional area
- (IV) 100% obstruction

Malacia (M)

Location

- (I) Perianastomotic-within 1 cm of anastomosis
- (II) Diffuse-involving anastomosis and extending beyond 1 cm

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location and severity of the airway pathology, timing post-transplant, and institution's bronchoscopy surveillance protocols. Anastomotic ACs after lung transplant can involve the anastomosis or distal airways and include those that typically develop within the first month of surgery (e.g., anastomotic infection, necrosis, or dehiscence) and those that develop later (e.g., excess granulation tissue, bronchomalacia, airway stenosis, and fistula) (6-9). Patients with ACs often require frequent bronchoscopic interventions, causing a significant impact on their quality of life (3).

Impairment of blood flow in the immediate post-transplant is believed to be the principal cause of most ACs after lung transplantation (7-13). The bronchial and pulmonary circulations supply blood to the lungs. The bronchial circulation is the systemic vascular supply to the lung, large airways, and branches down to the level of the terminal bronchioles (8,9). Seventy percent of the bronchial arteries usually arise directly from the thoracic aorta at the level of T5-T6 vertebra (10). There are usually three main bronchial arteries, one single right which originates from the intercostobronchial trunk, and two left that arise directly from the anterior surface of the thoracic aorta. During the lung harvest procedure, the bronchial blood supply is interrupted, leaving the bronchial vessels at the bronchial anastomotic site dependent on retrograde filling from the pulmonary artery circulation through communications in the submucosal plexus (4,10). Attempts to restore the bronchial circulation surgically are rarely performed. The timing for revascularization of the donor bronchus by the recipient bronchial circulation is typically 2 to 4 weeks, placing the anastomotic site at risk for ischemia (4,10).

Risk factors

Several factors have been related to an increased risk of anastomotic ACs. The major factors that increase the risk of ACs are those that increase anastomotic ischemia.

Surgical anastomosis techniques have an influence in the development of ACs. Several surgical techniques have been evolved over the years to improve the postoperative anastomotic ischemia, from a telescoped anastomosis, wrapping vascularized pedicles, end-to-end anastomosis, to bronchial artery revascularization (BAR), as described in the literature (6-8,14-20). The technique of tracheal anastomosis has been abandoned due to the high incidence of anastomosis ischemia and ACs seen (2,9,17). Reducing the length of the donor bronchus is key for minimizing

anastomosis ischemia. The current surgical techniques involve minimizing the length to within one to two cartilaginous rings (7,9,17). The biggest concern with telescoped bronchial anastomosis was a 48% rate of bronchial stenosis complications (14). The use of an end-to-end anastomosis, with the anastomosis performed closer to the secondary carina, is associated with a low incidence of complications and is the preferred surgical technique at most institutions (3,15). Few single-center publications have shown fewer rates of airway ischemia with the BAR technique (18,20). The suture techniques may also play a role in the development of ACs (17,21,22). Mulligan and colleagues described a lower rate of distal ACs from 12.2% to 4.4% in patients using a novel anastomotic technique, by performing the anastomosis at the secondary carina utilizing a combination of running and figure-of-eight sutures, minimizing donor bronchial ischemia (21). However, controversy remains regarding the optimal anastomotic technique.

Van De Wauwer and colleagues (17) found an increased risk of ACs post-transplant in patients receiving lungs from donors with prolonged (>50 to <70 h) ventilation support, and in tall recipients. Few studies found no differences in the rate of airway ischemia using donation after circulatory determination of death (DCDD) donors, compared to donation after neurologic determination of death (DNDD) donors (23,24).

It remains unclear the direct relationship between the extent of donor ischemic time and the incidence of ischemic ACs. The second anastomosis during a bilateral lung transplant is not at higher risk for ACs (25). Prolonged ischemic time observed with *ex vivo* lung perfusion is not associated with a higher risk of ACs (26). Nevertheless, prolonged ischemic times should be minimized due to its relation to lung transplant outcomes (27-29).

Patients who developed severe primary graft dysfunction (PGD) have a high rate of ACs (11,27-29). These patients have more extended mechanical ventilation and often require higher positive end-expiratory pressure (PEEP), which may decrease retrograde bronchial mucosa blood flow and increase the risk of airway ischemia (3,11,12).

Organ preservation techniques and perioperative management may also have implications for airway ischemia and complications. Antegrade and retrograde administration of preservation solutions have shown better results than organs perfused only with antegrade administration (30,31). Adding prostaglandin E1 was found to prolong preservation times to up to 24 h safely (32).

It remains unclear the role of airway infection in the development of ACs. However, preoperative and postoperative airway infections by both bacterial and fungal organisms have been related to high risk of ACs in some studies. Several organisms, especially fungi, including *Aspergillus*, *Candida*, *Rhizopus*, and *Mucor* species, have been associated with the development of ACs such as dehiscence, bronchial stenosis, and fistula formation (22,33,34).

Several studies have demonstrated that using steroids pretransplant or early postoperative did not show any deleterious effects on the anastomotic site healing (25,35). The use of mammalian target-of-rapamycin (mTOR) inhibitors, such as sirolimus, in the early post-transplant period, have been associated with an increased incidence of dehiscence (36,37). It is recommended to avoid mTOR inhibitors until at least 90 days after transplant.

Classification and management of ACs

Stenosis

Bronchial stenosis typically occurs within the first two to nine months but has been reported to occur over a year after transplantation (7,12,22). Patients with bronchial stenosis can present with dyspnea, cough, or wheezing, have declining flow rates on spirometry with abnormal flow-volume loop patterns, post obstructive pneumonia, or be asymptomatic and incidentally found on routine surveillance bronchoscopy. Central airway stenosis (CAS) is defined as stenosis at the bronchial anastomosis site or within 2 cm of the anastomosis. Distal airway stenosis (DAS) involves the airways distal to the anastomosis or the lobar bronchi. The incidence of DAS is 2.5–3% in the limited literature (37,38). DAS affects more frequently the bronchus intermedius, causing what is known as vanishing bronchus intermedius syndrome (VBIS) (4). VBIS is associated with high mortality and mean survival of 25 months after the initial diagnosis (38).

Several treatment options are often employed include balloon bronchoplasty, endobronchial stent placement, laser therapy, electrocautery, argon plasma coagulation, and cryotherapy. These procedures are usually performed in combination. The treatment choice for bronchial stenosis varies depending on the location and severity of the stenosis, and the institution's availability of interventional bronchoscopy procedures and expertise.

Balloon dilation is often the initial interventional procedure for bronchial stenosis. Usually, multiple balloon dilation procedures are required overtime due to recurrent

airway stenosis and based on the severity of the patient's symptoms (39). Bronchial balloon dilation is frequently performed in combination with endobronchial stent placement (4,7,39,40).

Self-expanding metallic stents and silicone stents are usually reserved for cases of severe and refractory stenosis due to the high incidence of complications related to stents such as mucous impaction, granulation tissue formation, dislodgement, and migration (38–43). Case reports using both biodegradable stents, as well as lobar stents, exist, though more extensive prospective studies are needed to validate their safety and efficacy (42,43).

Cryotherapy, endobronchial electrocautery knife, or Neodymium-yttrium-aluminum-garnet (Nd:YAG) laser have been used in the management of bronchial stenosis after lung transplant (44).

Few centers have reported successful results using high-dose-rate (HDR) endobronchial brachytherapy as an option in patients who have refractory bronchial stenosis (45–47).

When attempts at balloon dilation and stenting fail, surgical strategies include retransplantation, lobectomy, wedge bronchoplasty of the bronchus intermedius, and isolated sleeve resection of the bronchus intermedius (48–51). This situation is rare, so reliable data on surgical outcomes are lacking.

Dehiscence

Dehiscence is believed to be the result of severe airway necrosis, and it is usually within one to five weeks after transplantation (52). The incidence of anastomotic dehiscence ranges between 1–10% (4,52). Dehiscence is associated with high mortality, and early diagnosis and intervention are essential. Chest computed tomography (CT) can detect defects in the bronchial wall, showing bronchial narrowing or extraluminal air (53). However, bronchoscopy remains the gold standard for the diagnosis and guides further management.

The management of bronchial necrosis and dehiscence depends on the severity of the necrosis and the presence of any associated complications. Conservative management with antibiotic treatment and surveillance bronchoscopy is indicated for necrosis, which affects only the bronchial mucosa but not the bronchial wall, and when no air-leak is present (54). For clinically significant bronchial anastomotic dehiscence, some experts suggest placement of an uncovered self-expanding metallic stent, which appears to facilitate healing by stimulating neo-epithelialization

(40,52). Surgical interventions like reanastomosis, flap bronchoplasty, or in rare cases, retransplantation, have been considered in patients who have severe dehiscence or have a failure to more conservative measurements. However, reconstructive surgical approaches for dehiscence have been risky and disappointing (55-57).

Tracheobronchomalacia (TBM)

A diagnostic criterion of greater than 50% reduction in the luminal caliber on expiration has been widely used for the diagnosis of malacia (58). In the lung transplant population, TBM can be classified as perianastomotic malacia, localized within 1 cm of the anastomosis site, and diffuse involving anastomosis and extending beyond 1 cm (5). Patients can present with symptoms similar to airway stenosis, with dyspnea, inability to clear secretions, recurrent infections, wheezing, and a 'barking' cough, which is unique to bronchomalacia. Declining flow rates on spirometry with abnormal flow-volume loop patterns showing a variable obstruction, more marked during expiration. Bronchoscopy is the gold standard for the diagnosis of TBM, demonstrating a dynamic visualization of the airway during expiration.

The management of TBM in transplant patients is similar to that of the nontransplant-related malacia. The decision to treat TBM depends on the severity of symptoms and the extent of airway collapse. If infection or rejection is present, specific treatment may provide symptomatic relief. Patients with moderate airway collapse may benefit from one or more of the following: airway clearance techniques (e.g., oscillatory device or percussion vest), maintenance of airway hydration with saline nebulizer treatments, mucolytics, and non-invasive ventilation (NIV) (59-61). If significant symptoms and functional impairment persist despite conservative medical management, endobronchial stent placement may improve symptoms by establishing and maintaining patency of the malacic airway segment (62,63). Silicone stents are generally preferable, as they are more easily repositioned. Surgical interventions, including resection, reconstruction, tracheoplasty, and retransplantation, are additional options (64,65). However, this situation is rare, so data on surgical outcomes in lung transplant recipients are lacking.

Summary

ACs after lung transplantation remain an important source

of morbidity and mortality despite significant advances in the surgical techniques, leading to increased cost and decrease quality of life. The true incidence of airway ischemic complications after lung transplantation remains unclear.

ACs might be prevented by early recognition of the airway pathology, using advance medical management, and interventional bronchoscopy procedures. The best therapeutic approach in the management of ACs after lung transplant is often limited due to the lack of adequate data and is usually individualized to center preference and based on the location of the airway pathology. The 2018 ISHLT universal lung transplant airway grading system will help to determine the true prevalence and outcome of airway pathology, allowing the creation of future management strategies.

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