Airway complications post lung transplantation

Nancy R. Porhownik

Purpose of review
Advancements in surgical techniques, immunosuppression, graft retrieval, and postoperative care of lung transplant recipients has led to a decline in the incidence of airway complications since the first lung transplant was performed in 1963. Although improved, these complications remain a source of morbidity and mortality for lung transplant recipients.

Recent findings
Identification and management of risk factors is ideal, although interventional bronchoscopy techniques have allowed management of many airway complications in a less invasive fashion. With current management, mortality related to airway complications is now the same as mortality in lung transplant recipients without airway complications.

Summary
This review summarizes the six major classes of airway complications post lung transplantation, with descriptions of radiographic findings and current management.

Keywords
anastomosis, bronchoscopy, dehiscence, lung transplantation, stenosis

INTRODUCTION

In 2010, there were over 3500 lung transplants reported worldwide, approximately 1000 single lung and 2500 double lung transplants. The most common indications for lung transplantation are chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension (www.ishlt.org/registries). Although the first lung transplantation was in 1963, early attempts were largely limited by anastomosis necrosis and dehiscence [1]. Advancements in surgical techniques, immunosuppression, and post-transplant care have since led to thousands of successful lung transplants. A decline in the incidence of airway complications is largely responsible for improved early survival rates in lung transplantation. Currently, airway complications are reported in 7–18%, with a related mortality of 2–4% and overall survival rates comparable to lung transplant recipients without airway complications [2,3]. There is a lack of standard classification of airway complications, which contributes to the variable incidence rates reported. Although vastly improved, these complications remain a source of morbidity and mortality in lung transplant patients.

Several risk factors have been identified for airway complications. These include donor bronchus ischemia, surgical anastomotic technique, airway infections, immunosuppression regimen, graft preservation, and recipient height [4,5]. The donor bronchus experiences ischemia after transplantation as the normal bronchial supply of blood is not typically re-established during the surgery [6]. Collateral circulation supplies the donor bronchus, but revascularization of the donor bronchus takes several weeks. Various surgical techniques have been developed with the goal of reducing airway complications at the anastomosis, included end-to-end and telescoping anastomoses, tissue wraps, shortened donor bronchus [7], and direct bronchial artery revascularization. There is no consensus in the transplant community; however, most centers perform end-to-end anastomoses without tissue wraps [8–10]. Classification systems for bronchial healing post lung transplantation have been developed to predict the later development of obstructive airway complications [11]. The most widely used classification devised by Courad grades airway healing based on

Department of Respiratory Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

Correspondence to Nancy R. Porhownik, MD, FRCPC, ABIM, University of Manitoba, RS315–810 Sherbrook St, Health Sciences Centre, Winnipeg, MB R3A 1R8, Canada. Tel: +1 204 787 2977; e-mail: nporhownik@exchange.hsc.mb.ca

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KEY POINTS

- Identification and management of risk factors for airway complications has led to reduced incidence when compared to the early era of lung transplantation.
- The bronchial anastomosis is the most vulnerable site for airway complications due to ischemia early post transplantation.
- Interventional bronchoscopy procedures offer successful and less invasive management options for many airway complications post lung transplantation.

the bronchoscopic appearance, and ranges from grade 1 (perfect mucosal healing) to grade 3 (extensive necrosis). Courad grade 3 findings are associated with a high incidence of airway complications compared to grade 1 or 2 findings [12]. Other identified risk factors included longer donor mechanical ventilation time before organ retrieval, recipient–donor height mismatch, severe primary graft dysfunction, acute cellular rejection, and positive-pressure mechanical ventilation early post-transplantation [4,13,14]. Acute kidney injury may be associated with increased rates of airway complications [15▪]. Early identification and antifungal therapy for *Aspergillus* infections may reduce the incidence of airway complications, although an optimal antifungal prophylactic strategy is not clear [16]. Sirolimus, used for immunosuppression post solid organ transplants, has been associated with high incidence of airway complications, and treatment with this medication is contraindicated until after the anastomosis has healed completely [17,18].

The most common airway complication post lung transplantation is airway stenosis. Other airway complications include airway infections, exophytic granulation tissue formation, anastomotic dehiscence, tracheobronchomalacia, and bronchial fistulae. Management of airway complications may include observation, antimicrobial/antifungal medications, interventional bronchoscopic procedures, and/or surgery. Retransplantation for intractable airway complications has been performed in small numbers, although outcomes are suboptimal [19]. Prevention by identification and treatment for risk factors is ideal, and surveillance bronchoscopy can identify airway complications before symptoms or more severe complications occur.

AIRWAY STENOSIS

The most common airway complication post lung transplantation is airway stenosis. Bronchial stenosis typically occurs within the first 2 to 9 months post-transplantation [5,20,21]. It can be symptomatic, with dyspnea, respiratory distress, pneumonia, or respiratory failure [22], or asymptomatic detected by declining peak flows or direct visualization by bronchoscopy [23]. Chest computed tomography (CT) scan is very useful in characterizing bronchial stenosis, particularly using three-dimensional reconstructions [24]. Compared to direct visualization via bronchoscopy, CT reconstructions may be more advantageous when planning interventions [25].

Two types are seen: stenosis at the anastomosis and distal to the anastomosis (segmental, nonanastomotic large airway stenosis). Nonanastomotic stenosis is rare, has been linked to acute cellular rejection, and is presumably related to airway inflammation and injury [5]. The most common site of nonanastomotic stenosis is the bronchus intermedius (Fig. 1). The bronchus intermedius is particularly prone to ischemia following lung transplantation. A severe form, called the vanishing bronchus intermedius syndrome (VBIS), is a complete atresia of the bronchus intermedius [26]. This rare complication is associated with high morbidity and mortality [27]. Chest X-ray findings of VBIS included collapsed right middle lobe, lower lobe, or both lobes. Postobstructive pneumonia can also be detected on plain film chest X-ray. Direct visualization of the stenosis by bronchoscopy remains the gold standard for diagnosis.

Options for treatment of bronchial stenosis include several endoscopic procedures, including balloon dilatation, cryotherapy, electrocautery, laser, brachytherapy, and stent placement. Balloon dilatation is relatively safe, although may require repeated procedures for moderate to severe stenosis [28,29]. It is typically the first intervention for symptomatic stenosis. For stenting, silicone stents are generally preferred, allowing removal of the stent. Stents in the bronchus intermedius may be problematic due to possible obstruction of the right upper lobe orifice or restenosis at the upper part of the stent. Modified Montgomery T-tubes have been used to avoid occlusion of the right upper lobe [30]. Serious complications of these stents are rare, and after removal of stents, airways typically remain patent and lung function remains improved for as long as 2 years [31▪]. However, these stents can migrate (Fig. 2) or block adjacent bronchi. In these instances, covered metallic stents may be more efficacious, as long as they are removed before they granulate in the airway. Self-expandable metallic stents are usually removed under general anesthesia by rigid bronchoscopy, although more recently have been successfully retrieved by flexible

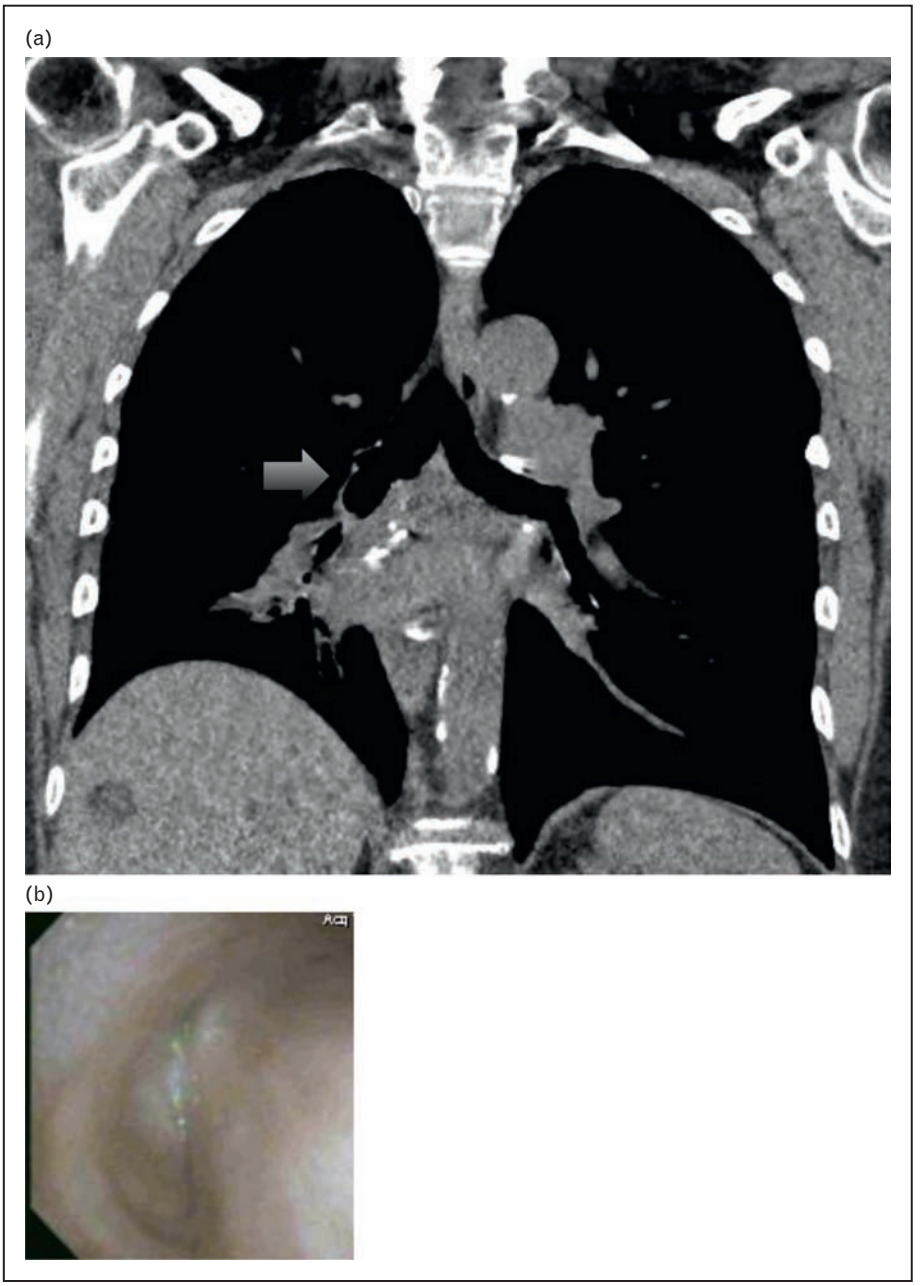

FIGURE 1. Stenosis distal to right anastomosis in patient with double lung transplant for pulmonary fibrosis. (a) Chest CT sagittal view, demonstrating stenosis (arrow). (b) Endoscopic view of bronchus intermedius. CT, computed tomography.

bronchoscopy using conscious sedation [32]. One pilot study successfully used biodegradable stents for treatment of bronchial stenosis, which may avoid the need for permanent stenting [33]. Surgery is reserved for when less invasive strategies fail, and may include lobectomy [34], pneumonectomy [35], reconstruction of the bronchial anastomosis, sleeve resections, or retransplantation [36].

INFECTIONS

Airway infections are both a complication and also a risk factor for subsequent airway complications post lung transplantation. Infections can involve the whole airway, such as a bronchitis or tracheitis, or involve the anastomosis specifically. Several factors predispose the bronchial anastomoses to infection. Reduced blood flow, immunosuppression, and retained secretions can create an optimal environment for bacteria and fungi to grow [37]. Bacteria present in either the donor or recipient bronchus at the time of transplantation can predispose to postoperative recipient infections [3]. *Aspergillus* infections at the anastomosis can be particularly devastating. Early infections may be asymptomatic, and are typically identified at surveillance

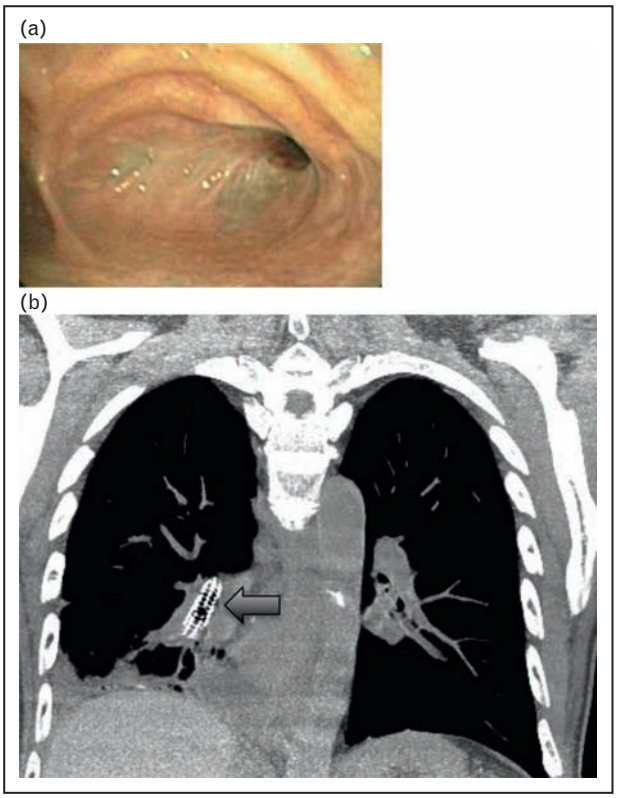

FIGURE 2. Right mainstem bronchus stenosis in patient 2 years post double lung transplantation for emphysema. Endobronchial stent migrated distal to right lower lobe subsegment (not seen endoscopically) (a) Endoscopy view of right mainstem bronchus. (b). Chest CT sagittal view, showing migrated stent (arrow). CT, computed tomography.

bronchoscopy. Up to 20% of post-transplantation patients will develop *Aspergillus* infection, either tracheobronchitis or anastomotic infection [16]. Rarely, *Aspergillus* airway infections become invasive. There are no specific radiographic findings, and it can be difficult to discern colonization from active infection. More commonly, they predispose the airway to subsequent bronchial complications [38]. Management includes antifungal therapy and may also include debridement of necrotic tissue.

EXOPHYTIC GRANULATION TISSUE

Granulation tissue formation at the site of the anastomoses is expected; however, growth of excessive tissue, particularly when it narrows the airway lumen by 25% or more, may cause respiratory symptoms or postobstructive pneumonia [3]. Significant stenosis caused by proliferative granulation tissue at the anastomosis has an incidence of 7–24%, and typically occurs within the first 3 months post-transplantation [39▪]. Airway infection with *Aspergillus* may increase granulation tissue formation [14]. Airway trauma and manipulation may also predispose to exophytic granulation tissue formation [40]. Chest CT may show the obstructing granulation tissue in the bronchi. Treatments include observation or debridement, although recurrence is common [40]. More recently, intraluminal brachytherapy has been effective for recurrent hyperplastic tissue after lung transplantation [39▪].

NECROSIS AND DEHISCENCE

Anastomotic dehiscence is difficult to treat and is associated with higher mortality [41]. At the anastomotic site, the mucosa first develops necrosis visible by flexible bronchoscopy. CT scans cannot reliably detect mucosal necrosis. Some necrosis is expected post-transplantation, due to donor bronchus ischemia; however, surveillance bronchoscopy can monitor for signs of healing or progression to dehiscence.

Anastomotic dehiscence may be partial or complete. The reported incidence of dehiscence is 1–10% [42], although extensive bronchial wall necrosis is rare, approximately 1.6% [3]. Radiographic findings of dehiscence may include pneumomediastinum, pneumothorax, including persistent pneumothorax with indwelling chest drains, subcutaneous emphysema, bronchial wall defects, or collections of peribronchial air or fluid at the site of dehiscence (Figs 3 and 4). Small airway irregularities and linear air pockets less than 4 mm anterior to the anastomosis are expected findings in lung transplants with telescoping anastomoses [21]. Chest X-rays can demonstrate findings, but are not reliable [43]. Chest CT is more useful for prognosticating, planning interventions, and monitoring healing after interventions [44]. Bronchial wall defects of 4 mm or less have excellent clinical outcomes [45].

Management of mucosal bronchial necrosis without dehiscence may be conservative, with antimicrobials with or without chest drains to optimize lung expansion. Self-expanding metallic stents placed by fiberoptic bronchoscopy may be used for more severe necrosis to stimulate localized neoepithelialization [44,46]. For necrosis involving the bronchi with partial dehiscence, fibrin glue can be applied to the defect, usually followed by a bare metal stent. If interventional bronchoscopic interventions fail, or if the dehiscence becomes complete, patients may require surgical repair or pneumonectomy. Complete dehiscence is associated with high morbidity and mortality, often secondary to sepsis [2].

TRACHEOBRONCHOMALACIA

Tracheobronchomalacia is a 50% or more narrowing of the airway during expiration due to the

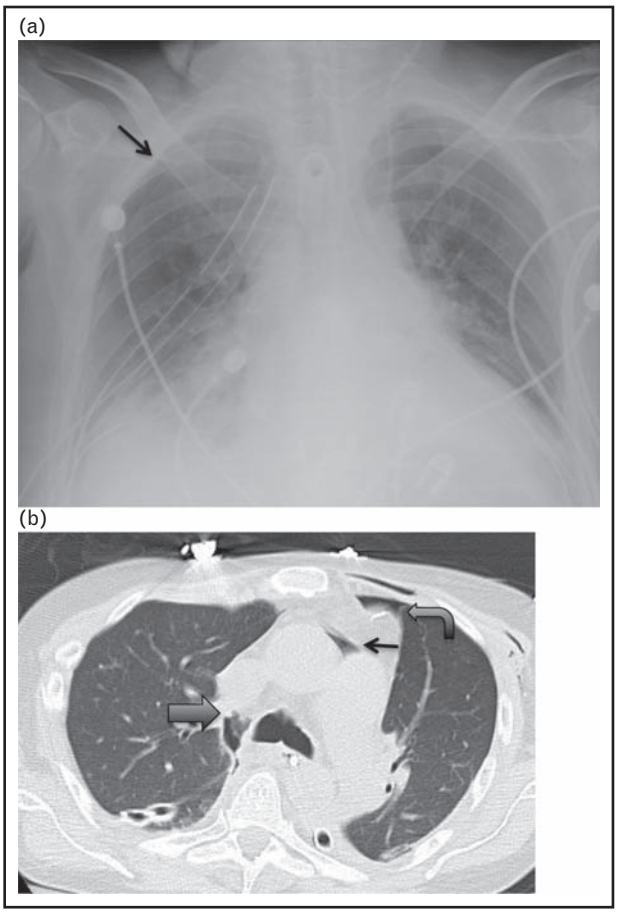

FIGURE 3. Mechanically ventilated patient 1 week post double lung transplantation for emphysema with bilateral partial anastomotic dehiscence. (a) Chest radiograph demonstrating right pneumothorax (arrow). (b) Chest CT demonstrating air collection at the right anastomosis (large arrow), left pneumothorax (curved arrow), and pneumomediastinum (small arrow). CT, computed tomography.

loss of structural integrity of the airway walls. Cartilaginous injury due to infection or postoperative bronchial ischemia is the presumed mechanism of airway injury, although it is not well understood [3]. It can occur diffusely or at the site of the anastomosis. The severity of tracheobronchomalacia is determined by the percentage narrowing of the airway lumen during exhalation, although the large airways can collapse in healthy patients and the identification of large airway dynamic collapse on imaging or direct visualization should always be correlated with clinical symptoms [47]. Although chest CT with inspiratory and expiratory views can be diagnostic, direct visualization of the airway with flexible bronchoscopy is the generally accepted means of diagnosis. Management may include observation, nocturnal continuous positive airway pressure, or in severe cases, placement of an endobronchial silicone stent [3,41]. Surgical repair is very rarely performed.

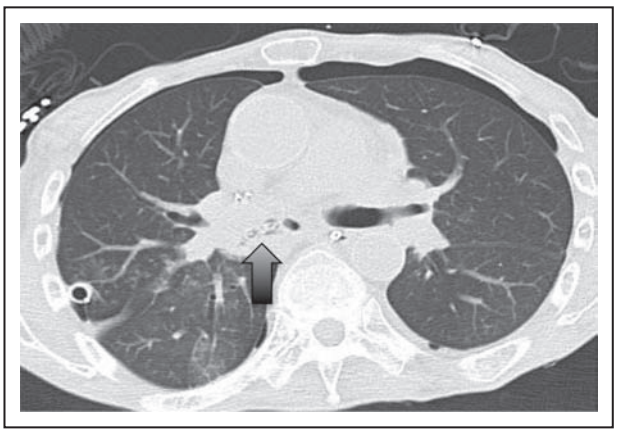

FIGURE 4. Chest CT in mechanically ventilated patient 10 days post double lung transplantation for emphysema, bilateral bronchial dehiscence demonstrating air–fluid collection at the site of the right anastomotic dehiscence (large arrow) and bilateral pneumothoraces. CT, computed tomography.

FISTULAE

With high associated morbidity and mortality, fistulae from the bronchus to the pleura, mediastinum, and vascular structures are rare complications. Bronchopleural fistulae typically present with a persistent air leak from chest drains, new pneumothorax, subcutaneous emphysema, respiratory distress, or hypotension [48]. They are treated by drainage of the pleural air and fluid collections, and antibiotics. Small bronchopleural fistulae may be closed with fibrin glue, but larger fistulae may require a covered metal stent [3]. Silicone stents can increase the size of the fistula and should be avoided [46]. Surgery to directly close the fistula can be performed, and can include direct sutures, muscle plombage, omentopexy, or intercostal muscle and rib flap [49]. Fistulae to the mediastinum present with mediastinitis or mediastinal abscess, and carry a high mortality. Drainage of mediastinal collections with concurrent antibiotics is the standard therapy, although with few reported cases, optimal therapy is not clear. Surgery for mediastinal debridement may have a role in severe cases. Bronchovascular fistulae can form between the bronchus and the aorta, pulmonary artery, pulmonary vein, or left atrium [50]. Risk factors include *Aspergillus* infection and metallic stent erosion [50]. Complications include sepsis, massive hemoptysis, or air embolism, and patients with bronchovascular fistulae have high mortality rates.

CONCLUSION

Although less common than in the early era of lung transplantation, airway complications still lead to increased morbidity for lung transplant recipients. Options for treatment have increased significantly as techniques and experience with interventional bronchoscopy has evolved. Clinical suspicion, imaging, and surveillance bronchoscopy are tools in the identification of airway complications. Early identification and modification of risk factors for airway complications is ideal.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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