

Mucocilliary Dysfunction Associated With Lung Transplantation: Causes, Effects, and Therapeutic Strategies

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The first successful lung transplantation occurred nearly twenty years ago. Since that time, with the conquest of complex technical and immunologic obstacles, the procedure has rapidly become a feasible treatment for an increasing variety of advanced pulmonary diseases.^{1,2,3} Currently, allowing for differences among transplantation centers and their patient populations, actuarial overall survival at 1 and 5 years post-transplant is approximately 85% and 56% respectively.⁴ Despite progressively improving outcome statistics, lung transplantation remains a complex and perilous endeavor. Long-term survival remains elusive. Recognition of factors that contribute to poor prognosis facilitates development of rational strategies for more effective prevention and treatment. Complications associated with impaired pulmonary defenses, especially mucociliary dysfunction, are a major factor in poor outcomes but are amenable to therapy.

The decision to undergo lung transplantation requires a heroic physical, emotional, and financial commitment by both patient and family members. In addition to the high cost of the surgery itself, an estimated two-thirds of care costs are incurred after transplantation.⁵ If major complications do not occur, there is much to be gained. Current data indicates that good postsurgical outcomes largely reverse the energy and physical pretransplant deficits, and that those quality-of-life gains are sustained for at least several years.^{6,7} Unfortunately, for many patients, respite is absent or brief. Serious, often lethal post-surgical complications jeopardize both graft function and patient survival. Therapy to prevent or treat rejection results inevitably in profound impairments of the immunologic defenses. Traumatic disturbances of respiratory mechanics associated with the transplantation procedure itself diminish both pulmonary defenses and graft function. Loss of cough reflex and concomitant impairment of mucociliary function place immunocompromised individuals at high risk for recurrent pneumonia and bacterial colonization. Finally, chronic rejection, or bronchiolitis obliterans, eventually signals the beginning of the end for most pulmonary allograft patients. At 5 years post-transplant 65-75% of patients will have developed evidence of this progressively destructive, incurable disorder.^{8,9}

Transplant-related pulmonary complications not only prevent normal activity, but also involve considerable morbidity, expense, and dependence. Treatment strategies for these complications remain inadequate.

Lung transplantation radically challenges the homeostatic integrity of the recipient, and severely disrupts the vascular, nervous, and immune systems. To remove diseased native lungs, their blood vessels and nerves must be transected. Although important connections (airways, pulmonary arteries, and pulmonary veins) are re-established, all can develop subsequent problems. Because the bronchial arterial supply is *not* restored, however, the lungs must rely on a single, oxygen poor, arterial blood supply. Nerves are not regenerated. The transplantation of foreign tissue elicits an array of immunologic responses. To prevent host rejection of the graft organ, recipients require a finely tuned regimen of immunosuppressive therapy; the immune system must be suppressed but not destroyed.

Pulmonary complications affect every lung allograft recipient to at least some degree. Respiratory infection is the most frequent cause of death within six months of transplantation; progressive bronchiolitis obliterans is the major cause of mortality after six months.¹⁰ Regardless of the proximate cause of post-surgical pulmonary dysfunction, nearly all disrupt the pulmonary defense system, impairing mucociliary clearance of pathogen-laden secretions, promoting colonization with treatment-resistant organisms, and precipitating progressive, ultimately fatal pulmonary infection and fibrosis.

Risk factors for complications in lung transplantation patients are most conveniently categorized as perioperative, short-term, and long-term.

Perioperative pulmonary complications

Technical aspects related to surgery, as well as defects and incompatibilities associated with the graft organ account for most complications occurring within 72 hours of lung transplantation. Technical problems are highly idiosyncratic and cannot reliably be anticipated.

Adverse events associated with surgical interventions include:

- Pressure abnormalities related to stenosis at the pulmonary arterial anastomoses
- Pulmonary edema as a consequence of venous obstruction of the left atrial anastomoses, or with no apparent cause¹¹
- Bronchial anastomotic dehiscence
- Peri-surgical graft failure is a serious complication that occurs in approximately 15-20% of lung allograft recipients.¹² Although ischemic-reperfusion injury is the presumptive cause of primary graft failure, other factors, i.e. surgical trauma, lymphatic disruption, hyperacute rejection, and donor aspiration and pneumonia may contribute.
- **Ischemic-reperfusion injury:** Risk factors for reperfusion injury include prolonged ischemic time and problems with preservation. Lung denervation and disruption of lymphatic and bronchial circulations are also implicated. Supportive care may require prolonged mechanical ventilation: Resultant barotrauma and associated nosocomial infection is the immediate cause of death in the 30% of patients who do not survive this complication.^{13,14}
- **Pulmonary edema:** Pulmonary infiltrates occur perioperatively in most lung allografts; causes are multifactorial and management is complex.¹⁵
- **Hyperacute rejection:** Hyperacute rejection is an infrequent but devastating complication that occurs most frequently in cases of donor/recipient ABO blood group incompatibility and, less frequently, in recipients with pre-existing antibodies to common human leukocyte antigens (HLA)^{16,17} Preoperative antibody screening procedures, time permitting, can diminish the problem. Patients with positive antibody screening results typically receive a tissue crossmatch at the time of transplantation and, if indicated, plasmapheresis prophylaxis for hyperacute rejection.

Treatment is supportive, relying principally on assisted ventilation and, at many centers, extracorporeal membrane

oxygenation therapy (ECMO). Up to 60% of perioperative graft failure patients do not survive more than a few days.¹⁸ Survivors of severe perioperative complications experience protracted recovery periods and increased risk of poor outcomes. Prognosis parallels the severity of the challenges.

The most serious obstacles to long-term survival begin to appear after surgical wounds are healed.

Postoperative pulmonary complications: Early

The terms "early" or "acute" are used to describe complications that arise during the first 2-6 postsurgical months. Among them, airway complications, acute rejection, and infection are the major threats to early survival. Patients experiencing mild short-term challenges have a good chance for an extended respite from pulmonary debility.

- **Airway complications:** Improved surgical techniques have reduced the incidence of serious airway complications to less than 15%. Anastomotic stenosis remains the most frequent airway complication, and may occur weeks or months after surgery. Narrowing may be caused by fibrous stricture, granulation tissue, or bronchomalacia; symptoms include clinically significant focal wheezing, poor pulmonary function, and recurrent lower respiratory tract infections. Airway complications are usually surgically correctable.¹⁹
- **Acute rejection:** Virtually all lung allograft recipients demonstrate some degree of acute rejection; many are never free of symptoms. Data suggest that the severity of acute rejection is proportional to the degree of HLA mismatching and its onset is inversely proportional to the intensity of the preventive immunosuppressant regimen.²⁰ Treatment poses a major therapeutic dilemma; increased doses of immunosuppressive agents control rejection but impair pulmonary defenses and increase risk for serious or fatal infection.²¹
- **Infection:** Infections are the leading cause of morbidity and mortality following lung transplantation; bacterial infections are most prevalent, but viruses, most lethally cytomegalovirus (CMV), and fungi, especially *aspergillus*, are also common.
- **Bacterial infection:** Bacteria are the most common pathogens responsible for both early and late morbidity and mortality after lung transplantation; the lung allograft is the principal locus of infection.²² Bacteria cause more than 60% of post-transplant infections; 75% are bacterial pneumonias occurring

within 60 days of surgery.²³ Approximately 25% of those experiencing early bouts of bacterial pneumonia go on to develop chronic purulent bronchitis.²⁴ Sinuses and upper airways of individuals with pre-existing bacterial colonization, most notably those with CF, will remain colonized after surgery, thus harboring a source of pathogens. Frequently, hospital-acquired bacterial infections, whether transmitted through donor lungs or originating in the recipient, are antibiotic resistant.

- **Viral infection:** Cytomegalovirus (CMV) infection, with an incidence of nearly 50%, poses a common, serious threat to lung transplant recipients; infection may be primary or secondary. Primary CMV, the most severe form, occurs in seronegative recipients receiving seropositive grafts; when fulminating pneumonia occurs, mortality may approach 50%.²⁵ Secondary CMV occurs in seropositive recipients, either as a result of reactivation of dormant infection or re-infection from the allograft; illness is generally mild. Treatment is available, but cure is not; both drug resistance and relapse are common.²⁶ Fortunately, ganciclovir has improved the outcome of CMV pneumonitis significantly, although some clinicians consider CMV infection a risk factor for BO. Pre-surgical prophylaxis may delay onset and attenuate severity of CMV infection.²⁷

Common respiratory viruses are emerging as increasingly important threats to lung transplant recipients.^{28,29} Another herpes virus, *Epstein-Barr*, is associated with development of the post-transplant lymphoproliferative disorders (PTLD) that appear in up to 10% of patients within the first year.³⁰

- **Fungal infections:** Approximately 10% of post-transplant patients demonstrate fungal infections, usually caused by *Aspergillus* and *Candida*.³¹ When fungal organisms are colonized in immunosuppressed patients, morbidity and mortality is significant. However, many such infections identified in BAL respond favorably to aggressive antifungal therapy. Manifestations of invasive disease include bronchitis, localized parenchymal infection, empyema, and disseminated disease. Invasive *Aspergillus* infections are extremely lethal and are commonly the terminal event in patients with complicated post-operative courses.³² Postoperative antifungal prophylaxis may be beneficial.³³
- ***Pneumocystis carinii*:** Owing to effective prophylaxis, *P carinii* is rarely seen in lung transplant patients; however, the disease occurs in nearly all

untreated patients.³⁴

- **Nerve damage:** Denervation of transplanted lungs and interruption of the pulmonary lymphatics contribute to altered pulmonary physiology and impaired cough function after lung transplantation.³⁵ Damage to the phrenic nerve, more common in heart-lung than in lung-only transplantation, weakens cough as well.³⁶ Surgical injury to the vagus nerve during heart-lung transplantation results in denervation below the level of tracheal anastomoses, abolishing the Hering-Breuer reflex, also impairing cough.³⁷ Likewise injury to the vagus nerve, by significantly delaying gastric emptying, increases risk for aspiration and pulmonary sequelae including inflammation, infection, bronchiectasis, and bronchiolitis obliterans.^{38,39} Lung denervation causes a ventilation/perfusion mismatch until autonomic functions are restored. Bilaterally denervated lung transplant recipients demonstrate an inability to maintain normal hypercarbic ventilatory responses.⁴⁰ This impairment could significantly increase susceptibility to respiratory failure in the presence of acute illnesses that increase ventilatory elastic impedance.⁴¹ Decreased mucociliary clearance has been demonstrated in the denervated lung.^{42,43}

Postoperative pulmonary complications: Late

Bronchiolitis obliterans syndrome: Bronchiolitis obliterans syndrome (BOS) is the most feared post-lung transplant complication; its incidence is high, progression rapid, and prognosis poor.⁴⁴ Chronic rejection (CR) and BOS are considered synonymous and the terms are used interchangeably.⁴⁵ Although the syndrome may appear as early as a few months after transplant, mean onset is 1-2 years. After five years, up to 75% of survivors are affected.^{46,47} The course of BOS development is variable; spontaneous improvement does not occur and treatment is largely unrewarding. Conclusively, a major mechanism leading to airway obliteration is immune mediated, and therapy is focused upon moderation of the immune response.^{48,49} Other factors may be important as well. Although Immunosuppressive protocols may slow the process, once BOS is established, retransplantation is the only alternative to death.^{50,51,52,53}

BOS is an obstructive defect manifested by a *fibrotic* pathologic process centered mainly in the small airways; it is thought to begin with an inflammatory event within the bronchioles.^{54,55} Sequelae of neutrophil recruitment, including the release of neutrophil oxidative and proteolytic inflammatory mediators (e.g., proteases and reactive oxygen species) contribute to damage to the bronchial epithelium and matrix.⁵⁶ Necrotic material accumulates in the lumen; mucus plugs develop. Fibroblasts proliferate and

collagen deposits are formed.⁵⁷ Progressive scarring occurs, resulting in concentric narrowing of the bronchioles.⁵⁸ Pulmonary function tests show largely irreversible airflow obstruction as evidenced by progressive decline in spirometric parameters.⁵⁹ Bronchiectasis and bronchomalacia complicated by infection are frequent concomitants of advanced BOS.⁶⁰

Although the etiology of BOS is poorly understood, there are several known risk factors.⁶¹ Well-recognized predisposing factors include:

- Frequency and severity of acute rejection episodes^{62,63,64}
- CMV pneumonitis^{65,66}
- Viral infections⁶⁷
- HLA antigen mismatches
- Development of human leukocyte antibodies (HLA).^{68,69}

Regardless of etiology, BOS predisposes patients to chronic lower airway colonization and recurrent infections with virulent bacteria, especially *S. aureus* and *Pseudomonas*. Indeed, more than 80% of bacterial pneumonias that occur later than 180 days after transplantation are associated with the presence of BOS.⁷⁰

Mucociliary dysfunction: A cause and effect of post-transplantation pulmonary complications

Pulmonary infection and acute rejection plague lung transplant recipients in the first weeks and months after surgery. In the long-term, infection and deterioration in lung function secondary to BOS pose major threats to survival. Histo-incompatibility and immunosuppressive therapy are the proximal causes of these complications, but impairment of mucociliary clearance (MCC) is the crucial concomitant factor.⁷¹

MCC is the principal mechanism to keep the bronchial tree free of mucus and cellular debris and defend it from infection. The cilia that line the bronchial epithelium beat regularly and continuously to propel mucus towards central airways and the larynx for expectoration. Ciliary beat frequency and the effectiveness of MCC are significantly impaired after lung transplantation, both in the immediate post-surgical period and in the long term.^{72,73}

Several factors have been shown to damage MCC including:⁷⁴

- Denervation
- Loss of bronchial arterial supply
- Factors related to the condition and preservation of the donor organ
- Immunological responses
- Effects of immunosuppressive therapy

- Consequences of repeated episodes of inflammation and infection.

All of these physiological alterations or insults contribute to progressive damage to the bronchial epithelial structure and compromise of MCC. Various mechanisms may have an additive effect on the reduced bronchial clearance characteristic of lung transplantation patients:⁷⁵

- Loss or impairment of cough function following transection of nerves
- Changes in mucus rheology related to denervation after lung transplantation⁷⁶
- Reduced clearance from unciliated peripheral airways related to parenchymal abnormalities in the graft organ
- Tracheal or bronchial anastomoses resulting in loss of normal epithelial surfaces, stricture or narrowing, and malacia from loss of cartilaginous support⁷⁷
- Abnormal ciliary function resulting from:
 - Previous episodes of pulmonary infection
 - Previous episodes of rejection
 - Quantitative or qualitative alterations in mucus; the autonomic nervous system or its mediators have been shown to affect:
 - Mucus production⁷⁸
 - Mucus rheology^{79,80}
 - Epithelial ion transport⁸¹
 - Adverse effects of immunosuppressive drugs⁸²

Universally, MCC and cough function are diminished in lung allograft recipients.

Clinical implications include:

Secretion retention and inflammation: In healthy individuals, inflammation plays an important role in overcoming infection and restoring lung health. In immunosuppressed pulmonary transplant recipients, however, microorganisms are poorly cleared and the inflammatory mediators accumulate in increasingly high concentrations, jeopardizing the integrity of the lung parenchyma. If unchecked, inflammatory disruptions in intercellular function progress until they result in the overproduction and subsequent retention of airway mucus, thus initiating the classic vicious cycle of pulmonary decline.⁸³

Whether initiated by pulmonary infection or other causes, excessive inflammatory response is a major contributing factor in the etiology of post-transplant complications.⁸⁴ The magnitude and persistence of inflammation in lung allograft

recipients contributes to the development of parenchymal lung destruction and pulmonary fibrosis. It is increasingly clear that inflammation can develop in the absence of infection and, in fact, may be the initial event that facilitates the onset of chronic infection.⁸⁵

Airway mucus: Response to inflammation

Airway mucus is a complex secretion that, together with the mucociliary transport system, serves primarily as a renewable and transportable barrier against inhaled or toxic agents. Disturbances of this defense mechanism, such as those caused by chronic inflammation, lead to mucus hypersecretion and its accumulation in the airways.

Retained secretions play at least two key roles in the pathophysiology of lung allografts:

- Retained secretions *physically* obstruct airways, leading to:
 - Infectious exacerbations and bacterial colonization
 - Immobilization of cilia
 - Pulmonary overinflation
 - Suboptimal ventilation/perfusion balance
 - Atelectasis
- Retained secretions *chemically* damage airways. Uncleared secretions contain high concentrations of cytotoxic inflammatory mediators, such as cytokines and leukotrienes, which can cause:
 - More mucus production
 - Increased concentrations of inflammatory mediators
 - Edema
 - Bronchospasm
 - Progressive parenchymal injury and destruction
 - Destruction of cilia
 - Irreversible fibrosis

Rationale for airway clearance therapy in lung allograft recipients

When MCC is impaired, instead of carrying away harmful matter, airway mucus is transformed into a vehicle for pulmonary destruction. In addition to the biophysical consequences of retained secretions, including airway obstruction and impaired gas exchange, the biochemical properties of inflammatory mucus are hazardous. Inflammatory mucus, characterized by neutrophil infiltration, results in increased protease activity. Significant mucus hypersecretion, alterations in mucus rheology, impaired mucus absorption, and damage to the mucociliary apparatus is the result.⁸⁶ In addition, toxic byproducts of inflammation precipitate rheological changes in airway mucus, making it thick, tenacious, and less

clearable by cough.⁸⁷ In the presence of chronic infection, hypersecretion and inflammation of the bronchi and bronchioles contribute to airflow obstruction by effecting decreases in the caliber of airways.⁸⁸ Typically, small airways fill, and eventually plug, with large quantities of purulent mucus. Retained mucus promotes establishment of bacterial colonies in those airways, thus setting up a relapsing and remitting course.⁸⁹ Histological examination of bronchial tissues demonstrates alterations in squamous epithelium, cilia, and associated structures.⁹⁰

In lung allograft recipients, the biophysical and biochemical consequences of chronic inflammation, mucus hypersecretion and altered mucus rheology accelerate the rate of pulmonary decline, compromise quality-of-life, and hasten the onset of BOS and graft failure. Accordingly, there is a persuasive rationale for preventing prolonged contact of small and large airways with "toxic" mucus.

Airway clearance treatment modalities

Mucociliary clearance may be augmented by techniques for improving coughing and airway clearance. Mobilization of secretions may be accomplished by a variety of techniques and devices. The active-cycle of breathing technique uses alternate periods of breathing control, thoracic expansion exercises, and huffing with an open glottis in place of coughing.⁹¹ Autogenic drainage is a method using three different levels of breathing in a controlled fashion.⁹² The Flutter[®] device promotes mucus mobilization with a combination of positive expiratory pressure and airway oscillation at the mouth.⁹³ Positive expiratory pressure uses collateral ventilation to mobilize secretions with a mask or mouthpiece apparatus.⁹⁴ However for lung transplant recipients who do not have the energy, lung capacity, or respiratory muscle strength for techniques that depend on forced expiration (e.g., the Flutter[®] device, active cycle of breathing), or positive end-expiratory pressure devices (e.g., PEP mask), options are limited to chest physiotherapy via percussion and postural drainage (P&PD) or high-frequency chest wall oscillation (HFCWO).

Chest physical therapy

CPT is an airway clearance technique that combines manual percussion and vibration of the chest wall by a caregiver, strategic positioning of the patient for mucus drainage, and, in unconscious patients, suctioning techniques. Typically, a treatment session consists of manual percussion for 3-5 minutes on each of nine specific thoracic regions while assuming appropriate drainage postures. Suctioning is performed between percussion periods. The technique, sometimes called percussion and postural drainage (P&PD), is based on the theory that percussion to various areas of the chest and back transmits

shock waves through the chest wall, which loosen secretions in the airways.⁹⁵

High-frequency chest wall oscillation

Underlying theory

HFCWO applies rapidly oscillating compressive forces externally to the thorax generating forces within the airways that dislodge mucus from the bronchial walls, decrease the viscosity of secretions, and create repetitive cough-like shear forces that mobilize mucus towards central airways where they can be cleared by expectoration or suctioning.^{96,97}

A device called the The Vest™ Airway Clearance System, manufactured and distributed by Advanced Respiratory, St. Paul, Minnesota, administers HFCWO therapy. The system consists of an inflatable vest connected by hoses to an air-pulse generator. The generator rapidly inflates and deflates the vest from 5-25 times per second, compressing and releasing the chest wall. This process is called high-frequency chest wall oscillation (HFCWO).

HFCWO distributes the oscillating compressive forces evenly over the thorax and thence to the lungs. This large contact area when multiplied times the pressure waveform produced by the device results in a large total oscillating force applied to the thorax. *This is very different from CPT* where the percussive forces are delivered sequentially and are concentrated in the relatively small contact area of a person's hand during each impact.

Patient's individual needs vary greatly. The success of an airway clearance program depends upon a careful evaluation of the status of each patient's MCC deficits, including cough function, respiratory muscle strength, pulmonary capacity, and exercise tolerance. Choice of modality should be determined by a clear definition of therapeutic goals, patient's motivation, psychological status, caregiver availability, and desire for independence. An inverse relationship exists between treatment adherence and burden of treatment; selection of a modality most appropriate for the individual is crucial.

Improving outcomes for lung allograft recipients

Although lung transplantation surgical procedures have improved steadily, preventive or treatment stratagems for the many subsequent complications have not kept pace. Future improvement in immediate and long-term survival after lung transplantation will largely depend on prevention or control of infection and subclinical rejection.

Many respiratory complications associated with lung transplantation are preventable or treatable. To prevent or

modify risks imposed by routine complications of thoracic surgery, including prolonged endotracheal intubation, retained secretions, and atelectasis, aggressive airway clearance therapy should be essential component of the postsurgical regimen. In lung allograft recipients, pulmonary defenses, including cough reflex, mucociliary clearance and immunologic function are permanently impaired. Individuals with significantly diminished secretion clearance function require an aggressive, lifelong regimen of bronchial hygiene including frequent airway clearance therapy to prevent or mitigate infection, to preserve lung function, to slow the process of progressive lung disease, and to avoid or reduce the need for intravenous antibiotics, risky modifications of immunosuppressive therapy, and retransplantation or death.

Individuals willing to accept the risks and obligations of lung transplantation deserve the best possible chance for a good outcome. Interventions to moderate the frequency and intensity of early lung infections and acute rejection episodes will not only reduce early morbidity and mortality, but may also delay onset of BOS. For that reason, every effort must be made to recognize and understand the causes of graft failure and to identify and implement useful therapies.

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