Overview of Clinical Lung Transplantation

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Since the first successful lung transplant 30 years ago, lung transplantation has rapidly become an established standard of care to treat end-stage lung disease in selected patients. Advances in lung preservation, surgical technique, and immunosuppression regimens have resulted in the routine performance of lung transplantation around the world for an increasing number of patients, with wider indications. Despite this, donor shortages and chronic lung allograft dysfunction continue to prevent lung transplantation from reaching its full potential. With research into the underlying mechanisms of acute and chronic lung graft dysfunction and advances in personalized diagnostic and therapeutic approaches to both the donor lung and the lung transplant recipient, there is increasing confidence that we will improve short- and long-term outcomes in the near future.

The worldwide burden of pulmonary diseases continues to increase and now ranks firmly among the leading causes of death (Lozano et al. 2013). Since its introduction in the early 1980s, lung transplantation has matured into a successful therapy for selected patients with end-stage lung disease, because of careful investigation into donor management, organ preservation, recipient management, and immunosuppression (Christie et al. 2012). This review provides an overview of modern clinical lung transplantation and anticipated future directions.

HISTORY

Attempts at lung transplantation have occurred as early as 1946 when Vladimir Demikhov, a Soviet scientist, attempted single-lung transplantation in a dog (Langer 2011). This transplant ultimately failed from bronchial anastomotic

dehiscence, and difficulties with this anastomosis would plague clinical lung transplantation for the next 40 years. Henri Metras, in 1950, reported the first successful dog lung transplant and the first bronchial artery and left atrial anastomoses (Metras 1950). In a nonhuman primate model, Haglin et al. (1963) performed lung reimplantation and showed that these lungs were able to maintain function postoperatively, despite denervation. On June 11, 1963, Hardy et al. (1963) reported the first human lung transplant; however, the patient died from kidney failure after 18 d. The first real survivor during this early era of lung transplantation was a patient of Fritz Derom's in Belgium (Derom et al. 1971). This patient, however, survived only 10 mo. The failure of this early experience in clinical lung transplantation can be summarized by inadequate immunosuppression and difficulties with the bronchial anastomosis.

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The advent of cyclosporine brought about significant improvements in patient survival following liver and kidney transplantation (Calne et al. 1978). This led to a resurgence of interest in heart/lung transplantation in Stanford and lung transplantation in Toronto (Starzl et al. 1981). The first successful combined heart–lung transplant was completed by Reitz and colleagues and showed that a grafted lung could survive and function in a recipient (Reitz et al. 1982). Research performed by Cooper’s group in Toronto showed that corticosteroid use appeared to be a significant factor in the weakness of the bronchial anastomosis (Goldberg et al. 1983). With the use of cyclosporine, corticosteroid use could be reduced, leading to improved bronchial healing. In 1986, the Toronto Lung Transplant Program reported the first successful single-lung transplantations for two patients with pulmonary fibrosis (Cooper et al. 1987). This team went on to perform the first successful double-lung transplant, first with an *en bloc* technique that used a tracheal anastomosis, then evolving to the bilateral sequential transplantation technique that not only improved airway healing, but also had the additional benefit of avoiding cardiopulmonary bypass, if desired (Patterson et al. 1988). This technique remains the standard technique in use to this day.

INDICATIONS AND CONTRAINDICATIONS TO LUNG TRANSPLANTATION

The indications for lung transplantation can be broadly separated into the following main categories of end-stage lung diseases: obstructive lung disease, septic lung disease, fibrotic lung disease, and vascular lung disease. Of these categories, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), interstitial pulmonary fibrosis (IPF), and primary pulmonary arterial hypertension make up the most common indication in each category, respectively (Christie et al. 2012). Lung transplantation for pulmonary malignancy has also been shown to be effective in highly selected patients (Machuca and Keshavjee 2012).

The current International Society for Heart and Lung Transplantation (ISHLT) and also the

American Thoracic Society (ATS) selection criteria include appropriate age, clinically and physiologically severe disease, ineffective or unavailable medical therapy, substantial limitations in activities of daily living, limited life expectancy, adequate cardiac function without significant coronary disease, ambulatory with rehabilitation potential, acceptable nutritional status, and satisfactory psychosocial profile and emotional support system (Orens et al. 2006). Patients who undergo lung transplantation subject themselves to lifelong immunosuppression and surveillance. Thus, candidates for lung transplantation who have smoking or drug dependency, psychiatric issues affecting compliance with postoperative care, or absence of a reliable social support network will generally not be listed for lung transplantation. Previous malignancy, particularly in the 2 yr leading up to potential transplantation, is also a contraindication because of the need for lifelong immunosuppression. Indeed, although immunosuppression will potentiate infection, chronic infection is an intrinsic part of septic lung diseases and creates a challenge in these patients. In cystic fibrosis patients, nontuberculous mycobacterial, multi-drug-resistant bacteria, and *Aspergillus* are commonly isolated (Helmi et al. 2003; Gilljam et al. 2010). An effort is made to eradicate or at least minimize these organisms before and following transplantation. Moreover, in the presence of septic lung disease, a bilateral lung transplant is the only operation that can be performed because leaving a septic lung in a patient to be immunosuppressed is not advisable. The replacement of both organs removes the burden of infectious organisms and allows for successful transplantation in the presence of most septic lung conditions. One notable exception is the *Burkholderia cepacia* complex (Bcc), an organism with a significant negative impact on posttransplant survival (Murray et al. 2008). In multiple reports, patients infected with Bcc, particularly the subspecies *Burkholderia cenocepacia*, have a clearly worse survival than those without. Consequently, some transplant centers consider Bcc infection an absolute contraindication to transplantation, but this remains controversial (Chaparro et al. 2001).

Patients with significant dysfunction of other vital organs also represent potential contraindications to lung transplantation. Owing to age, general prevalence, and smoking, cardiac dysfunction is the most common concomitant organ dysfunction in the lung transplant population. Noninvasive and invasive cardiac testing is performed during workup to ensure adequate cardiac function, and concomitant coronary arterial bypass grafting can be performed at the time of lung transplantation if the left ventricular function is preserved (Patel et al. 2003).

Historically, age >65 has been considered a relative contraindication to lung transplantation given the propensity toward worse outcomes in that group. However, 7.7% of lung transplants performed in the recent era (2004–2011) were in patients >65 (Christie et al. 2012). Another 21.6% were performed in patients between 60 and 65. Careful assessment of comorbidities, rather than age alone, determines candidacy for transplantation.

DONOR LUNG ALLOCATION

In the United States, lung allocation was initially based on wait times alone with no consideration of disease severity or potential benefit. Many recipients were placed early on the waiting list in order to accrue time, but when a lung was ultimately made available, the patient may not have yet deteriorated to a point requiring transplantation. On the other hand, patients in more dire need of a transplant would often not survive long enough to accrue enough time to be offered a graft. In 2005, a new strategy for lung allocation was introduced (Egan et al. 2006) known as the lung allocation score (LAS). This score is conceptually based on the degree of need for a transplant and the probability of post-transplant survival. To calculate this, a measure of urgency (expected number of days lived without a transplant during an additional waitlist year) and a measure of survival following transplantation (expected number of days lived in the first year posttransplant) are calculated using statistical models based on the patient's clinical and physiological characteristics. The urgency measure is subtracted from the benefit measure

and then normalized to give an LAS. Higher scores are allocated lungs sooner. Since the introduction of the LAS system, waitlist times have decreased, and the number of transplants has increased (Iribarne et al. 2009). Moreover, LAS scores have gradually increased, representing the increasing urgency of patients getting listed.

PEDIATRIC LUNG TRANSPLANTATION

Lung transplantation for children has also evolved into acceptable therapy (Wells and Faro 2006). In the United States, more than 100 children currently await lung transplantation. The indications for pediatric lung transplant differ from those for adults and stratify based on age. Children <1 yr of age suffer largely from congenital defects such as congenital heart disease, surfactant dysfunction, and pulmonary vascular disorders (Benden et al. 2013). Cystic fibrosis (CF) becomes the primary indication after 1 yr of age, with the majority of adolescent lung transplants being performed for CF. Identifying acceptable candidates for pediatric lung transplantation is difficult, particularly in the very young. The worldwide experience is limited in this population, and the natural history of many of these congenital diseases is not always clear. Moreover, readiness of the parents to embark on the demanding preoperative and postoperative care necessary of pediatric lung transplantation must be carefully assessed. Allocation of organs to pediatric recipients uses the LAS system in patients 12 yr of age or older (Sweet 2009). For patients under 12 yr of age, the United States uses a two-priority system in addition to wait times (Colvin-Adams et al. 2012). Patients meeting criteria (Table 1) are priority 1 and receive consideration for graft allocation first following geographic and blood-type criteria considerations. In the very young, where isohe-magglutinins have not yet developed, ABO-in-compatible lung transplantation has been shown to be a feasible option (Grasemann et al. 2012).

BRIDGING TO LUNG TRANSPLANTATION

Often, patients needing lung transplantation become critically ill before a set of donor organs

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Table 1. Pediatric priority 1 criteria

Respiratory failure as defined by one or more of the following:
Continuous mechanical ventilation
Fraction of inspired oxygen (FiO ₂) >50% to maintain saturation levels of >90%
An arterial or capillary PCO ₂ of >50 mm Hg or a venous PCO ₂ of >56 mm Hg
Pulmonary hypertension as defined by any of the following and on medical therapy:
Pulmonary vein stenosis involving three or more vessels
Suprasystemic PA pressures
Cardiac index 2 L/min/m ²

Data from Colvin-Adams et al. (2012).

is available. Traditionally, intubation and ECLS (extracorporeal lung support) were the sole modalities available for bridging to transplantation. In the past few years, novel artificial lung technologies have been developed that allow critically ill patients to be maintained temporarily over months (Fischer et al. 2006). One of these devices is the Novalung, a hollow fiber oxygenator with a uniquely low *trans*-device perfusion resistance. This allows for pumpless function from the arterial to venous circulation. Patients in respiratory failure can be divided into those with hypercapnic respiratory failure, those with hypoxemic respiratory failure, or those with both. Because removal of CO₂ requires only a low membrane flow on the order of 0.5–1 L/min, this can be achieved using the pumpless arteriovenous cannulation. An extension of this strategy can be applied to patients with pulmonary hypertension awaiting transplantation. By inserting the device between the pulmonary artery and the left atrium, the right heart can be unloaded into the Novalung device (Strueber et al. 2009). This provides a decompressing and oxygenating shunt. This treatment strategy unloads the right ventricle, allowing it to recover, and also leads to recovery of renal and hepatic dysfunction. All of this has dramatically improved the survival to and after lung transplantation for patients with primary pulmonary arterial hypertension (22% waitlist mortality pre-Novalung, 0% waitlist mortality

post-Novalung utilization) (de Perrot et al. 2011).

For patients who suffer from more than pure hypercapnic respiratory failure, full venovenous or venoarterial ECLS is a better choice. Novel bicaval dual lumen cannulas, such as the Avalon cannula, allow venous–venous ECMO to be started via a single cannulation site in the neck (Wang et al. 2008). In case series, patients awaiting lung transplantation have avoided intubation and could continue an exercise regimen while on ECMO (Garcia et al. 2011; Cypel and Keshavjee 2012).

DONOR SELECTION

Once a donor has been identified and allocated to a potential recipient, the donor organs must be checked for quality and procured from the donor. Like all of solid organ transplantation, lung transplantation is even more limited by the number of available donor organs. Shortages in lung transplantation, however, are compounded by a low utilization rate of offered donor organs. The United Network for Organ Sharing data reports that lungs were used from only 1708 of 8143 deceased donors in 2012—a utilization of only 21% (National Data 2012). As a comparison, 7419 of those same donors were kidney donors. The current International Society for Heart and Lung Transplantation (ISHLT) criteria outlining an ideal donor are based on strict criteria established during the development of lung transplantation (Table 2). Although this has helped establish safe clinical

Table 2. ISHLT criteria for lung acceptance

Age <55 yr
ABO compatibility
Clear chest radiograph
PaO ₂ >300 on FiO ₂ = 1.0, PEEP 5 cm H ₂ O
Tobacco history <20 pack/yr
Absence of chest trauma
No evidence of aspiration/sepsis
No prior cardiopulmonary surgery
Sputum gram stain—absence of organisms
Absence of purulent secretions at bronchoscopy

From Orens et al. (2003); reproduced, with permission, from the authors.

lung transplantation, this combination of stringent donor criteria coupled with an increased susceptibility of donor lungs to injury leads to a conservative and low utilization rate (Orens et al. 2003).

DONOR LUNG INJURY

Currently, the largest pool of donor organs is those retrieved from brain-death donors. In these donors, cessation of neurologic function results in a legal definition of death (Wijdicks et al. 2010), but organs remain viable for a period of time owing to preserved cardiac function and ICU support. Although this situation is seemingly ideal for organ transplantation, many factors can contribute to donor lung injury during the process of donor death and subsequent donor maintenance in the intensive care unit (ICU). Direct trauma, aspiration, pneumonia, and complications of ICU care such as ventilator-induced lung injury, atelectasis, oxygen toxicity, and volume overload are all common causes of injury. More importantly, it is well recognized that the process of brain death itself can injure potential donor organs. Following brain death, a systemic inflammatory response known as a “cytokine storm” transpires. Increased proinflammatory cytokines have been found in organs following brain death in rodent models (Takada et al. 1998) and in brain-dead patients (Lopau et al. 2000), and lung injury similar to acute respiratory distress syndrome (ARDS) can occur as a result of this systemic inflammation following brain death. A second “storm” that occurs following brain death is the catecholamine storm. In an attempt to protect cerebral perfusion during brain death, the body releases a large amount of catecholamines. This surge of catecholamines causes significant systemic hypertension, which results in elevated left-sided heart pressures and consequent interstitial edema and sometimes even alveolar hemorrhage in the lung, resulting in a state known as neurogenic pulmonary edema. This generally precludes the use of the lungs for transplantation because of poor oxygenation. However, neurogenic pulmonary edema is a leaky capillary syndrome that is fully recoverable. This is

one area where removal of the lung from the inflammatory milieu of the brain-dead donor and a period of time for recovery and removal of extravascular water with ex vivo lung perfusion has had a significant impact on donor lung utilization as described below.

DONATION AFTER CARDIAC DEATH

As an alternative source for lungs, some transplant programs have begun to reexplore the use of donation after cardiac death (DCD) (Kootstra et al. 2002; Steinbrook 2007). Because the majority of patients succumb as a result of cardiac arrest, the use of DCDs could potentially open a completely new pool of donor organs of such magnitude that ultimately the entire demand could be met. Renewed interest in the potential use of lungs from DCDs followed a series of experiments in dogs by Egan and co-workers in the early nineties (Egan et al. 1991; Ulicny et al. 1993). His group showed that lung cells remain viable for a certain period after circulatory arrest (Alessandrini et al. 1994; D’Armini et al. 1994). The lung is the sole solid organ that is not dependent on perfusion for aerobic metabolism but rather uses a mechanism of passive diffusion through the alveoli for substrate delivery (Keshavjee et al. 1992; Date et al. 1993; Egan 2004; Van Raemdonck et al. 2004).

At the First International Workshop on DCDs in Maastricht in the Netherlands in 1995, four types of donors were identified, so-called Maastricht categories (Table 3) (Kootstra et al. 1995). Categories I (dead on arrival) and II (unsuccessful resuscitation) comprise the *uncontrolled* donors. Categories III (awaiting car-

Table 3. Maastricht categories of donation after cardiac death

I	Dead on arrival to hospital	Uncontrolled
II	Unsuccessful resuscitation	Uncontrolled
III	Awaiting cardiac arrest	Controlled
IV	Cardiac arrest following brain death	Controlled
V	Cardiac arrest in a hospital inpatient	Uncontrolled

Data from Sánchez-Fructuoso et al. (2000).

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diac arrest) and IV (cardiac arrest in brain-dead donor) include the *controlled* donors. A fifth category, cardiac arrest in a hospital inpatient, has recently been added (Sánchez-Fructuoso et al. 2000).

Several centers worldwide have now adopted DCD programs in their clinical routine of lung transplantation, and most reported series deal with controlled donation after withdrawal from life support (category III) (Erasmus et al. 2006; Butt et al. 2007; Oto et al. 2007; Van Raemdonck et al. 2008). The total reported experience with this category now amounts to more than 100 patients worldwide. The majority of reported series using category III DCDs have comparable results to a series of donation after brain death (DBD) patients. A recent review of the U.S. experience using data retrospectively collected from the UNOS database has shown an overall survival after lung transplantation of 94%, 94%, 94%, 94%, and 87% at 1, 3, 6, 12, and 24 mo, respectively, for recipients receiving lungs from DCD donors, compared with 92%, 88%, 84%, 78%, and 69%, respectively, from DBD (Mason et al. 2008).

DONOR LUNG EVALUATION

Evaluation of an offered donor lung block is largely a clinical process. Other than blood group and organ size matching, the majority of the evaluation is relatively subjective and occurs at the time of retrieval (Boasquevisque et al. 2009). Before opening the chest, a chest X-ray is taken and a bronchoscopy performed to exclude gross infection or anatomical abnormalities. The gas exchange capacity of the donor lungs is assessed with an oxygen challenge. Once the chest is open, the surgeon performs a final gross physical evaluation by macroscopic observation and palpation to assess lung compliance and edema and to exclude intrinsic lung disease, areas of contusion, pneumonic infiltrates, or nodules. Observation of the ventilated lungs during deflation is used to further assess pulmonary compliance. If the lungs are deemed usable, they are retrieved and sent to the transplant center for implantation. Evaluation of the DCD donor is similar, but functional testing is limited

to before cardiac arrest; therefore, lung evaluation is less assured.

ORGAN PRESERVATION

In the initial early experience of lung transplantation, donors were brought into an adjacent operating room, and the donor lungs were deflated and topically cooled in situ for preservation (Cooper et al. 1987). The lungs were then stored deflated and submerged in hypothermic saline solution and placed on ice for hypothermic preservation. Despite short ischemic times, immediate postoperative care was fraught with significant postoperative primary graft dysfunction and poor preservation of the pulmonary and bronchial microcirculation. Only with subsequent advances in lung preservation has lung transplantation been able to be established as a clinical routine. Modern lung preservation is a continuum that begins at the time of declaration of death and ends after reperfusion in the recipient. In the preretrieval phase, care is taken to maintain euolemia and to avoid ventilator barotrauma. A methylprednisolone bolus of 1 g is given to the donor as an anti-inflammatory agent to mitigate brain-death-induced inflammation and also in part to replace any steroid deficiencies (Follette et al. 1998; Venkateswaran et al. 2008). At the time of retrieval, the lungs are prepared for transport flushed with a preservation solution and inflated with oxygen. Use of an extracellular-type flush preservation solution with low potassium, coupled with glucose and dextran, was found to be best for prolonged cold preservation (Keshavjee et al. 1989, 1992). This has become the standard of lung preservation in the majority of lung transplant programs. PGE₁ (prostaglandin E₁) is a vasodilator that is given before flush to reduce the pulmonary vascular resistance in order to help produce a homogeneous flush. It also has anti-inflammatory properties useful for lung preservation and reperfusion injury (De Perrot et al. 2001). A retrograde in situ lung flush is also performed with the same solution, again to improve the homogeneity of the flush (Varela et al. 1997; Van De Wauwer et al. 2009). The lungs are inflated with 50% oxygen before their removal from

the body in order to maintain the delicate alveolar structure and to provide oxygen for metabolism (Van Raemdonck et al. 1997). This is an important distinction of lung preservation as compared with other organ preservation in that the lung is stored in an *aerobic hypothermic ischemic* state so that aerobic metabolism can continue during the storage phase, albeit at a reduced rate.

Recently, a novel strategy of clinical lung preservation has been developed by our group. Known as ex vivo lung perfusion, lungs are continuously perfused anterograde with an acellular perfusate and ventilated with room air with an ICU ventilator at normothermia (Cypel et al. 2008). An oxygenator fed with a hypoxic gas is used to deoxygenate the perfusate and add CO₂ to the perfusate. We have shown that donor lungs can be preserved for at least 12 h safely using this method. Because the lungs will function using this strategy of preservation, they can be further evaluated as to their suitability for transplantation, but, more importantly, can be treated actively to improve their performance (Cypel et al. 2009). DCD lungs, given the less than optimal opportunity for lung evaluation after cardiac arrest, can greatly benefit from this technique. Marginal lungs can also be resuscitated during this time using existing and future therapies (Yeung et al. 2012). In a recent clinical trial, marginal lungs normally rejected for transplantation were evaluated and resuscitated using ex vivo lung perfusion and then transplanted with resulting outcomes equivalent to contemporaneous controls (Cypel et al. 2011, 2012). Because the large majority of offered donor lungs are rejected because of injury, this expansion of the donor pool is significant and could greatly help meet the need for donor lungs. In the future, we envision that retrieved lungs could be sent to organ evaluation and repair centers for final assessment and treatment for repair before distribution to recipients around the country. A case report describing the retrieval of injured lungs at one center, EVLP repair at a second center, and then transplantation at a third center across multiple political jurisdictions acts as a proof-of-concept for this approach (Wigfield et al. 2012).

LUNG TRANSPLANT PROCEDURES

Different lung transplant procedures have been developed to meet certain situations. Most familiar are: the single-lung transplant, where either a left or a right lung is transplanted into a recipient and the contralateral native lung is left in place; and the bilateral lung transplant, where both lungs are transplanted. The decision to transplant one or two lungs depends on the indication for transplantation and recipient factors, as well as donor availability. Emerging data suggest that bilateral lung transplantation results in prolonged survival because it provides more functional lung tissue as a buffer against lung dysfunction (Thabut et al. 2008; Weiss et al. 2009). For the same reason, marginal donor organs are often more likely to be used when implanted as a bilateral lung transplant. However, double-lung transplantation is a more complex operation, which necessitates a longer operative time that needs to be balanced against potential added morbidity. In addition, in jurisdictions where donor availability is severely lacking, transplanting two recipients with single lungs may reduce waitlist mortality. Specific indications also call for double-lung transplantation. Because of the presence of infection, septic lung disease patients require a double-lung transplant to prevent infection of the lung graft from the native lung. Although not an absolute indication, bilateral lung transplantation for vascular lung disease with elevated pulmonary arterial pressures is best because it avoids difficulties with hemodynamic instability and severe primary graft dysfunction postoperatively.

Although the abovementioned lung transplant procedures are by far the most common, alternative procedures have been developed that can be used in unique situations. The donor lung can be nonanatomically volume-reduced to fit into a smaller recipient (Noirclerc et al. 1992). For larger size discrepancies, an adult donor lung can be downsized anatomically to implant a lower or upper lobe on either side in a smaller recipient (bilateral lobar transplant) (Starnes et al. 1994). Another innovative operation is the split left-lung bilateral lobar transplantation technique, which allows for a large

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donor to donate a single left lung to a smaller recipient or child, where the left upper lobe and left lower lobe are implanted to the right and left chest, respectively (Couetil et al. 1997). Living donor lobar transplantation is applied in jurisdictions where the legal and cultural climate is not conducive toward deceased donor transplantation, such as in Japan. In this situation, the right lower lobe is removed from one donor and transplanted into the right chest, and the left lower lobe is removed from another donor and transplanted into the left chest. Date and colleagues in Japan have a large experience with this technique and have shown excellent outcomes (Date et al. 2004). Experience in the United States with this technique has waned since the introduction of the LAS allocation system.

Combined heart/lung transplantation is reserved for cases in which irreversible heart disease occurs in conjunction with irreversible lung disease. In most cases, severe right heart dysfunction can be reversed after isolated lung transplantation, and thus heart/lung transplantation is generally reserved for patients with left heart dysfunction.

SURGICAL TECHNIQUE

In general, most lung transplant centers avoid the routine use of cardiopulmonary bypass (CPB) during lung transplantation. For single-lung transplantation, the diseased lung is excised and the new lung implanted while the patient is supported on the contralateral native lung. If the patient cannot be supported this way because of significant hypoxia, hypercarbia, or hemodynamic instability, then CPB is instituted.

Bilateral lung transplants are performed as sequential single-lung transplants via a clamshell incision or bilateral anterolateral thoracotomies if preferred and technically feasible (Taghavi et al. 1999). The sequential transplant strategy not only allows for the avoidance of CPB in most (60%–75%) cases, but also avoids a tracheal anastomosis, which was used in the original *en bloc* double-lung transplant operation (Griffith et al. 1994). The tracheal anastomosis was fraught with anastomotic complications related to the precarious blood supply of

the graft airway at that level. Following chest opening, mobilization of each of the native lungs is performed. The lung with the poorest function is removed first, and implantation of the first graft begins. Once complete, this first allograft is perfused and ventilated. The recipient is then dependent on this lung's function as the contralateral side is removed and the second lung implanted. Hemodynamic instability, elevated pulmonary arterial pressure, or hypoxemia necessitates the use of cardiopulmonary bypass. Ultimately, only ~25% of recipients with no pulmonary vascular disease will require CPB (de Hoyos et al. 1993).

POSTOPERATIVE CARE

Care of the lung recipient in the immediate postoperative period focuses on ventilatory and hemodynamic support and weaning. In uncomplicated cases, ventilator weaning can proceed quickly over the first 6–12 h. Because of increased vascular permeability and severed lymphatics of the transplanted lung, development of some element of pulmonary edema is not uncommon. Therefore, attempts to minimize pulmonary capillary wedge pressure and central venous pressure are made while balancing for the need to maintain systemic perfusion (Pilcher et al. 2005). Often, vasopressors and inotropes are used rather than infusion of volume.

The major fear postoperatively is failure of the transplanted lung to function. Such a scenario can be mimicked by volume overload, cardiac dysfunction, pneumonia, aspiration, antibody-mediated rejection, pulmonary thromboembolism, or technical complications such as occlusion of venous outflow (de Perrot et al. 2003). In the absence of these conditions, primary graft dysfunction (PGD) becomes the diagnosis of exclusion. PGD is the major cause of morbidity and mortality in the first 72 h following transplantation. It can be considered the expression of all injury acquired by the lung while in the donor through to the time of reperfusion. Generally, this injury presents as pulmonary edema resulting in decreased compliance and ineffective oxygenation. This pulmonary edema results from increased permeability of pulmo-

nary capillaries and alveolar damage and is reminiscent of ARDS. The ISHLT has published a grading system for PGD similar to that for ARDS (Christie et al. 2005). Patients are scored on this grading system at the time immediately posttransplant, and then at 24, 48, and 72 h posttransplant. Those who have PGD 3 persisting to the 72-h point have the worst short- and long-term outcomes (Whitson et al. 2006).

Treatment of PGD is supportive. Careful use of sedation and paralysis, close hemodynamic monitoring, and avoidance of nosocomial pneumonia are important. Nitric oxide has been shown to improve oxygenation, reduce pulmonary artery pressure without affecting systemic pressure, and shorten the duration of mechanical ventilation in case series (Date et al. 1996; Ardehali et al. 2001). Its primary effect is likely due to improvement in V/Q matching because NO is delivered to alveoli that are ventilated, although NO also has important anti-inflammatory properties related to neutrophil, macrophage, and platelet function (Coggins and Bloch 2007). PGE₁ infusion can also be helpful in treating severe PGD because it down-regulates inflammation in the acutely reperfused lung. When maximal treatment fails, ECLS should be started as a bridge to recovery (Fischer et al. 2007). ECLS can allow for gas exchange while avoiding harsh ventilation strategies that can further injure the graft. Although the experience is limited, the literature suggests that ECLS should be started early in the onset of severe graft dysfunction, usually within 24 h of lung transplant severe PGD, and be limited to a short trial of 4–7 d (Fiser et al. 2001).

POSTOPERATIVE IMMUNOSUPPRESSION

Lung transplant immunosuppression generally consists of a three-drug regimen with the exact composition being center dependent. A calcineurin inhibitor (cyclosporine or tacrolimus), a nucleotide blocking agent (azathioprine or MMF), and corticosteroids make up the three drugs. Induction therapy, the use of a potent immunosuppression agent to deplete T cells such as anti-IL2R antibodies, anti-CD52 antibodies, or antithymocyte globulin, is controver-

sial in lung transplantation. Use of induction therapy is thought to promote strong early immunosuppression during the time when graft rejection is most likely to occur and may allow for a less toxic maintenance regimen going forward. Although prospective, randomized, placebo-controlled trials did not show significant benefit, and large RCTs do not currently exist, registry data show that ~50% of lung transplant programs use induction therapy based on logical extrapolation from the demonstrated benefit of induction therapy in other organ randomized control trials (Hachem et al. 2008; Hartwig et al. 2008).

OUTCOMES

Although lung transplantation has been shown to confer increased survival to patients with end-stage lung disease, survival following lung transplantation is still only ~50% at 5 yr (Christie et al. 2010). The major causes of death following lung transplantation vary with the time following transplantation. Thirty-day mortality is generally related primarily to surgical issues, donor lung preservation, and primary graft dysfunction (PGD) (Studer et al. 2004). Infectious causes, malignancy, and chronic lung allograft dysfunction (CLAD) predominate in the subsequent posttransplant period. Despite significant improvements in short-term outcomes owing to improved preservation and surgical technique, the long-term survival after lung transplantation remains at around a 50% 5-yr survival because of the development of CLAD (Christie et al. 2012). Next to the shortage of donor organ supply, CLAD remains the most significant challenge to the long-term success of lung transplantation and should be a focus of research in this area.

CHRONIC LUNG ALLOGRAFT DYSFUNCTION

CLAD is a recent term coined to describe the increasingly complex and heterogeneous conditions causing long-term lung dysfunction following transplantation (Sato 2013). Historically, chronic lung dysfunction was thought to pre-

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sent only as bronchiolitis obliterans syndrome (BOS), where the progressive development of obliterative bronchiolitis led to a fall in FEV₁ and ultimately to graft loss. A novel subtype of BOS (now CLAD) was first recognized as a distinct entity in 2005 (Pakhale et al. 2005) and then subsequently functionally and histologically characterized in further detail by Sato et al. (2011, 2013). Now known as restrictive allograft syndrome (RAS), this form of CLAD presents histologically as fibrosis in the peripheral lung tissue rather than in small airways, resulting in a decline in total lung capacity in addition to a decline in FEV₁. This solidified the understanding that all chronic lung dysfunction is not BOS and set the stage to focus the attention of the lung transplant community on exploring various different potential forms of CLAD and the potential multiple underlying contributing pathophysiologic mechanisms. Other phenotypes of CLAD have now been described, including neutrophilic allograft syndrome (NRAD), and fibrous BOS (FBOS) (Vanaudenaerde et al. 2008).

The pathogenesis of BOS was initially thought to represent a type of chronic rejection, that is, an alloimmune-dependent process, but alternative alloimmune-independent processes are now thought to contribute to the development of BOS and CLAD in general. Primary graft dysfunction, viral and bacterial infections of the graft, and gastroesophageal reflux and aspiration have been shown to predispose a graft toward CLAD (Davis et al. 2003; Botha et al. 2008; Snyder et al. 2010). It is thought that these processes, in addition to damaging the graft directly, activate innate immune processes, which then propagate the injury via the adaptive immune system (Palmer et al. 2005). Autoimmune processes have also been shown to play a role. Exposure of typically cryptic antigens such as type-V collagen and K- α 1 tubulin during the lung transplant process may help drive the CLAD process (Burlingham et al. 2007; Goers et al. 2008).

Treatment options for CLAD are currently limited. The use of azithromycin in a randomized controlled trial has been shown to slow the progression of CLAD, potentially through its anti-inflammatory, antibiotic, or promotility ef-

fects, but the exact mechanism is unclear (Yates et al. 2005; Murphy et al. 2008; Vos et al. 2011). Switching classes of immunosuppression may be of some benefit in slowing progression of the disease, but no therapy has yet been shown to reverse the disease process. The only definitive treatment for end-stage CLAD is retransplantation, but limited organ availability and generally poorer outcomes render this approach controversial.

Although CLAD limits long-term survival, survival alone is an incomplete measurement of transplant benefit. To patients, quality of life (QOL) can be as important as quantity of life, and lung transplantation can almost be considered a type of treatment in which, in some instances, quality of life is improved even if little or no gain in quantity of life occurs. Multiple longitudinal studies have recently shown improvements in QOL following lung transplantation, some as early as 3 mo posttransplant (Gross et al. 1995; Cohen et al. 1998; Lanuza et al. 2000). More than 90% of lung transplant survivors are satisfied with their decision to undergo transplantation.

CONCLUDING REMARKS

Lung transplantation has become firmly established as a treatment of end-stage lung disease. Increased adoption of lung transplantation is currently limited by the availability and suitability of donor organs. Unique to lung transplantation is the low utilization rate of the existing donor lungs because of the frequent findings of lung injury. The recently developed ex vivo lung perfusion preservation strategy is now established in Toronto and in selected centers in Europe, with trials in the United States underway. This technique improves evaluation and also allows for the delivery of therapy to treat injured donor lungs in a targeted fashion allowing for their use. Exploration and development of ex vivo repair strategies tailored to each donor lung will be important toward a “personalized medicine” approach to the diagnosis and treatment of the donor lung.

The major factor limiting positive long-term outcomes remains the development of

CLAD. Although the pathogenesis is still not completely elucidated, it is well accepted that this represents graft dysfunction resulting from multiple etiologies. Many novel mechanisms have recently been recognized to contribute toward CLAD, and subtypes with different clinical courses have been identified. Further research into the underlying mechanisms and development of clinical strategies to mitigate the development of CLAD will transform lung transplantation into a sustained and long-term treatment of lung disease.

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