History of Lung Transplantation

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Early Surgical History

In 1947, Vladimir P. Demikhov performed the first experimental lung transplant in dogs. Over the next few decades, numerous accomplished surgeons performed experimental lung transplants which resulted in improved surgical techniques and better understanding of cardiopulmonary physiology. Hardy et al. [2] performed approximately 400 experimental canine lung transplants before performing the first lung transplant on June 13, 1963, at the Medical Center of the University of Mississippi. The patient survived 17 days, dying from renal failure and infectious complications. Until 1983, approximately 40 lung transplants were performed with survival varying from hours to days. However, on November 14, 1968, Derom et al. [3] performed a single left lung transplant in a 23-year-old man with silicosis, surviving 10 months and dying from infectious complications (pneumonia from *Pseudomonas* and *Candida*). In 1983, Dr. Cooper of Toronto General Hospital performed the first single-lung transplant resulting in long-term survival of approximately 7 years, in a patient with pulmonary fibrosis [4]; in 1986, Dr. Patterson performed a double-lung transplant in a patient with emphysema [5], with a survival of nearly 16 years.

In the 1990s, Starnes [6] performed the first living (right lobar) donor transplant in a 12-year-old child with bronchopulmonary dysplasia at Stanford University Medical Center.

Heart-lung transplantation was first performed in 1968 by Cooley at Texas Children's Hospital [7] in a 2.5-month-year-old girl with pulmonary hypertension, surviving only 14 hours. At various institutions, three combined heart-lung transplants were performed over years with poor survival. The first long-term survivor from a combined heart-lung transplantation was performed at Stanford on March 9, 1981, by Reitz [8] for primary pulmonary hypertension surviving 5 years.

Over the decades, the field of lung transplantation has overcome major obstacles including surgical techniques, immunosuppressant regimen, lung donor preservation, and infectious prophylaxis. However, lung transplantation as a viable treatment option for end-stage lung diseases lagged behind other organ transplantations for many years.

Airway Complications and Immunosuppression

During the initial years of lung transplantation, dating back to the 1940s, experimental lung transplants were unsuccessful primarily related to airway dehiscence, reported at a 60–80% complication rate [9, 10]. Airway complications, primarily due to dehiscence of the bronchial anastomosis, continued to be a leading issue related to significant morbidity and mortality. The initial theory was that ischemia of the donor bronchus was due to the lack of restoration of the arterial systemic blood supply (bronchial arteries) at the time of transplantation. Therefore, it became clear that the viability of the donor bronchus was initially dependent upon retrograde collaterals from the pulmonary arteries (less oxygenated blood). Various centers introduced the possibility of bronchial artery revascularization with successful outcomes [11, 12]. However, given the technical difficulties leading to longer operative time, this technique has not been universally accepted, and large series are lacking. In addition, bronchial artery regeneration was evident in experimental lung transplants in canine models [13, 14].

Over the ensuing decades, other complications, including infections and lack of proper immunosuppressant regimen, continued to plague the field of lung transplantation [15]. With the advent and success with the use of cyclosporine in

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renal transplant, there was a renewed interest in advancing the field to lung transplant [16]. The Toronto Lung Transplant Group, led by Cooper and colleagues, began canine experimental lung transplants to investigate risk factors that were felt to be major contributors to bronchial dehiscence [17]. Initial immunosuppressant regimens included azathioprine and corticosteroids. In 1981, early practitioners discovered that steroids led to poor bronchial healing with no effect from the azathioprine [18]. Reitz and colleagues performed the first successful heart-lung transplantation using cyclosporine, azathioprine, and prednisone [8]. Introduction of cyclosporine to the standing regimen of azathioprine and lower dosing of prednisone allowed the success of five single-lung transplants with idiopathic pulmonary fibrosis with no patients dying of airway complications [19]. In addition, Cooper and colleagues used omentopexy, a surgical procedure whereby the suture of the omentum to another organ increases arterial circulation, to improve bronchial collateral circulation and possibly alleviate narrowing distal to the airway anastomosis which was thought to be related to ischemia.

With success from single-lung transplants, Patterson et al. evaluated the possibility of en bloc double-lung transplant using omentum wrapped around the tracheal anastomosis [20, 21]. However, due to high rate of tracheal anastomosis necrosis, there was a 25% mortality, and 20% of patients developed delayed airway stenosis requiring intervention. This technique was, therefore, abandoned. Complications related to gastrointestinal ischemia with omental wraps, and other alternative surgical techniques using intercostal muscle or peribronchial tissue anastomosis wrap, did not gain traction within the field. With the advent of end-to-end anastomosis with excision of the donor bronchus just proximal to the takeoff of the upper lobe bronchus, near the secondary carina, airway complications were significantly reduced [22, 23]. Bilateral sequential lung transplantation was introduced by Kaiser and colleagues with minimal airway complications and significantly reduced early morbidity and mortality, similar to single-lung transplant procedures [24].

Preservation Solutions

Since the beginning of lung transplantation, donor lung preservation has been an instrumental element leading to more successful outcomes. Proper preservation of organs resulted in full physiological and biochemical function after transplantation by maintaining the anatomical barriers (e.g., alveolar-capillary barrier). Historically, intracellular fluid (e.g., Euro-Collins solution and University of Wisconsin solution) composition had been utilized for the preservation of donor lungs, as derived from the kidney and liver transplant experience. Through experimental animal models, Fukuse et al. concluded that standard Euro-Collins solution, containing high potassium concentration, compared to modified Euro-Collins solution (low potassium concentration) resulted in significant elevation in pulmonary vascular resistance, leading to possible damage to the vascular endothelium, further increasing the risk for ischemic reperfusion injury [25]. Further studies concluded that low-potassium dextran solution leads to improved preservation solution organ flush and ischemic storage [26]. Improvements in preservation solutions have led to reduced primary graft dysfunction. Okada et al. reviewed five clinical trials (four retrospective and one prospective non-randomized study) and concluded that low-potassium dextran solution was superior to Euro-Collins solution in graft preservation and early graft function [27].

Cytomegalovirus Prophylaxis

Historically, cytomegalovirus (CMV) has been an important contributor to morbidity and mortality in lung transplant recipients. It is important to differentiate CMV infection, defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen, versus CMV disease, defined by the presence of CMV infection with attributable symptoms and signs or evidence of tissue invasion, as this aids in the approach of treatment and outcomes. The incidence of CMV infection and disease in other solid organs (e.g., heart, liver and kidney) is approximately 9–35% [28]. In contrast, the incidence of both CMV infection and disease is higher in lung transplant population, approximately 40% [29]. Major risk factors associated with CMV disease are the serostatus (donor positive, recipient negative [D+/R−] being at the highest risk), the type of organ transplanted, and the immunosuppressive regimen used, including induction therapy [30]. In the absence of prophylactic antiviral therapy in renal transplant recipients, median time of onset of CMV infection (CMV pp65 antigenemia) was 35 days in all serostatus groups (except, seronegative donor and recipient, D−/R−) [31]. Through indirect, induced systemic inflammation from CMV replication within in the host (e.g., transplant recipient) and direct deleterious effects of CMV, CMV disease has been shown to be associated with acute and chronic allograft dysfunction [32–35].

Rubin et al. evaluated the optimal prophylaxis in solid organ transplant recipients (e.g., kidney, liver, and heart) for the prevention of primary cytomegalovirus with oral ganciclovir or oral acyclovir. The incidence of CMV infection or disease was significantly reduced in the ganciclovir group (32% vs. 50%, $P < 0.05$), within the first 6 months post-transplant [36]. Similar results were seen in lung transplant recipients comparing intravenous (IV) ganciclovir versus oral acyclovir until 90 days post-transplant. Cumulative incidence of all CMV infections (including seroconversion) was significantly reduced in the IV ganciclovir group (15% vs. 75%, $P < 0.033$) [37]. In an open, comparative study of 22 patients, Speich et al. evaluated the efficacy of oral ($n = 9$) vs. IV gan-

ciclovir ($n = 5$) for CMV prophylaxis in lung transplant recipients and comparative historical non-prophylaxed control ($n = 8$) group. One patient developed cytomegalovirus disease in the oral ganciclovir group, none in the IV group, and six in the non-prophylaxed group [38]. Limitations associated with ganciclovir formulations, including the low bioavailability of the oral preparation [39] and the patient inconvenience, cost, and catheter-related infections of the IV delivery route [40], led to the development of valganciclovir, an ester prodrug of ganciclovir. Valganciclovir, 900 mg/day, provides comparable plasma ganciclovir levels compared to those achieved with 5 mg/kg IV ganciclovir [39]. Its bioavailability (60%) is approximately tenfold higher than that of oral ganciclovir [39]. Studies have demonstrated the safety and efficacy of valganciclovir for CMV prophylaxis in solid organ transplant patients excluding lung transplant recipients [41]. Zamora et al. evaluated the efficacy and appropriate length of prophylaxis with valganciclovir for the primary prevention of CMV infection and disease in seropositive lung transplant recipients [42]. Consecutive lung transplant recipients ($n = 90$) received prophylaxis with valganciclovir (450 mg twice daily) to complete 180, 270, or 365 days, compared to historical group ($n = 140$) who received high-dose acyclovir (800 mg three times daily). Both groups initially received prophylaxis with IV ganciclovir (5 mg/kg daily) and cytomegalovirus immune globulin (CMV-IVIG), 30 days for seropositive recipients (D+/R+ and D−/R+), and 90 days for seropositive donors (D+/R−). CMV disease was significantly reduced in the valganciclovir group compared to acyclovir group (2.2% vs. 20%, $P < 0.001$).

Another evolution in the prophylaxis and treatment of CMV has been the use of cytomegalovirus immune. In 2010, Palmer et al. showed a decrease in CMV disease (4% vs. 32%, $P < 0.001$) and infection (10% vs. 64%, P 0.001), extending the valganciclovir prophylaxis period to 12 months versus standard 3 months. During the 6 months after study completion, a low incidence of CMV disease was observed in both groups [43].

Future understanding of the recipient's CMV-specific immunity may aid in developing the optimal duration of antiviral prophylaxis and sustaining prevention of CMV in this high-risk patient population [44]. However, the evolution of therapy to prevent and treat CMV-related complications has been an important step forward in improving the outcomes following lung transplantation.

Lung Allocation Score

Prior to May 2005, the allocation of lungs was based on accrued time on the waiting list. This resulted in disproportionately high mortality rates on the waiting list, mostly because there were no medical urgency parameters within the allocation system. Because the allocation system did not factor in severity of illness, patients with idiopathic pulmonary fibrosis (IPF) had an especially high mortality rate while on the waiting list. Recognizing this issue with respect to the IPF patients, in 1995 an exemption was put into effect that led to an additional 90-day wait-list credit for patients with IPF.

In response to the persistently increasing number of deaths on the transplant list, the US Department of Health and Human Services published in 1998 and implemented in March 2000 – the "Final Rule," which required the Organ Procurement and Transplantation Network (OPTN) to emphasize the broader sharing of organs, reducing waiting time as an allocation criterion and structuring a system for equitable organ allocation using objective medical criteria and urgency for allocation [45]. As a result, in 1998, the Lung Allocation Subcommittee of the OPTN Thoracic Organ Transplantation Committee was formed to structure an alternative lung allocation system in keeping with the goals of the Final Rule: (1) reduction of mortality on the lung waiting list, (2) prioritization of candidates based on urgency while avoiding futile transplants, and (3) reducing the importance of waiting time and geography in lung allocation within the limits of ischemic time [46].

In May 2005, OPTN changed the policy for donor lung allocation from a system that previously allocated based primarily on accrued waiting time on the list to a system that allocated lungs based primarily on a lung allocation score (LAS). The LAS is calculated from objective clinical data that predicts 1 year survival on the waiting list (without transplantation) and post-transplantation. Multiple factors, predictive of wait-list mortality and post-transplant survivability including diagnoses, were included in the LAS formula. The ultimate goals of the LAS are to (1) reduce the number of deaths on the lung transplant list, (2) increase transplant benefit for lung transplant recipients (avoiding futile transplants), and (3) ensure the efficient and equitable allocation of the lungs to active transplant candidates [46].

Donation After Cardiac Death and Ex Vivo Lung Perfusion

The relative scarcity of traditional brain-dead organ donors remains a most critical obstacle to ensuring the availability of organs to recipients with end-stage organ disease. Traditionally, the lungs are the lowest procured organs, approximately 15–25%, compared to all other transplanted organs [47]. As a result, several studies have shown that liberalization of the current standard lung donor criteria, also known as "marginal donor lungs," could achieve similar outcomes [48–50]. Emerging techniques for further increasing donor lungs include donation after cardiac death (DCD) and ex vivo lung perfusion (EVLP).

The first successful human lung transplant was performed by Hardy and colleagues in 1963 using an allograft from a

DCD [2]. Over the ensuing decades, the primary reason for the slow adoption of DCD lungs has been the concern for graft injury from prolonged warm ischemia time. Mason et al. reported on the retrospective review of the UNOS registry, from 1987 to 2007, analyzing the outcomes of 36 lung transplantations performed using DCD. Overall survival at 1 year post-transplantation was 94%, equivalent to the traditional donation after brain death [51]. Subsequently, single-center experience revealed similar outcomes [52–54]. Love and coworkers published long-term follow-up in a single-center experience [55]. Between 1993 and 2009, 18 recipients received lungs from DCD. Outcomes were compared with those recipients who received organs from brain-dead donors ($n = 406$). One, 3-, and 5-year survival rates ($P = 0.66$) and freedom from bronchiolitis obliterans syndrome ($P = 0.59$) were similar between groups. Incidence of primary graft dysfunction were similar ($P = 0.59$). Overall, DCD can expand the donor pool with similar outcomes compared to the traditional brain-dead donors.

In 2001, the utilization of EVLP in human lung transplantation using DCD was published [56]. Despite good physiological function of the transplanted lung until 5 months post-transplant, patient died from CMV infection. The University of Toronto published the largest series of lung transplants performed using EVLP with 58 EVLP cases resulting in 50 lung transplantations. The incidence of primary graft dysfunction was 2% in the EVLP group and 8.5% in the conventional transplant group ($P = 0.14$) with 87% survival at 1 year [57]. The development of EVLP systems allows for prolonged preservation of organ, ongoing assessment of physiological function (e.g., gas exchange, hemodynamics, ventilation), and reconditioning of injured organs. The latter is performed through high oncotic perfusate solution (dehydrating the lungs) and recruitment of the atelectatic lungs. Finally, EVLP can aid in the evaluation of DCD organs following procurement with assessment of graft function. The Toronto Lung Transplant Group published a detailed review of the step-by-step technique and assessment of donor pulmonary grafts placed on EVLP [58].

Conclusions

Although much progress has been made in the field of lung transplantation, there is still much that needs to be addressed. While surgical technique and basic early postoperative care has largely been well established, by far the biggest challenge to long-term success of lung transplantation continues to be how best to prevent the development of the bronchiolitis obliterans syndrome (BOS) and, when it occurs, how to slow the progressive loss of lung function associated with it. Although BOS research has focused on several different angles, some immunologic and some non-immunologic, no one single factor seems to explain its occurrence and the devastating effect it has on patient survival. Until BOS can be better understood, the long-term survival of lung transplant recipients will be less assured than that seen in other solid organ transplant recipients.

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