Review Article

Narrative review of the evolution of lung transplant

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Objective: To outline the important steps and major advances in the evolution of lung transplant in all its aspects and fields.

Background: The first successful human lung transplant was performed approximately six decades ago, but evolution has been slow. It was not until the past two decades that lung transplantation became a more routine procedure with predictable outcomes.

Methods: A comprehensive search of the medical literature using Ovid and PubMed search engines was conducted for progression of all aspects of lung transplantation, including surgical techniques, immunosuppression progression, donor selection criteria evolution, recipient criteria evolution, new technology used to support the patient prior and after transplant, along with donor organ management and the Lung Allocation Scoring (LAS) system variables and their impact on outcomes after lung transplantation.

Conclusions: Advancement has been multifactorial in all phases of lung transplantation: in the preoperative phase with better selection criteria, better nutrition, and better pulmonary and physical rehabilitation; in the perioperative phase with improvement of surgical techniques, immunosuppression drugs, development of mechanical circulatory support, and preservation technology; and in the postoperative phase with better understanding of immune rejection and better management of long-term complications. All these progressions have been fundamental to the current success of lung transplantation.

Keywords: Extracorporeal membrane oxygenation (ECMO); ex-vivo lung perfusion (EVLP); history; lung transplantation

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Introduction

Progression in lung transplantation has been slow, but outcomes have changed dramatically from a few days' survival in the first 20 years to excellent and more predictable outcomes nowadays. In 2019, the United Network for Organ Sharing (UNOS) reported an all-time record of 2,714 lungs transplants in the USA, which is a 7.3% increase from 2018 and over 4,000 worldwide (1). In 2020 the number of lung transplant cases in the USA was affected by the COVID-19 pandemic and dropped to 2,539 lung transplants. Lung transplantation has progressed exceptionally over the past 60 years in all aspects, including surgical techniques, donor and recipient selection criteria, revolutionary progression in immunotherapy along with new technologies that have improved the quality of the donor lung and support the recipient in the preoperative period. All of this has resulted in a meaningful growth in lung transplantation and improved long-term survival. In this review we will focus on the major steps of this evolution in all areas of lung transplantation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-21-11/rc).

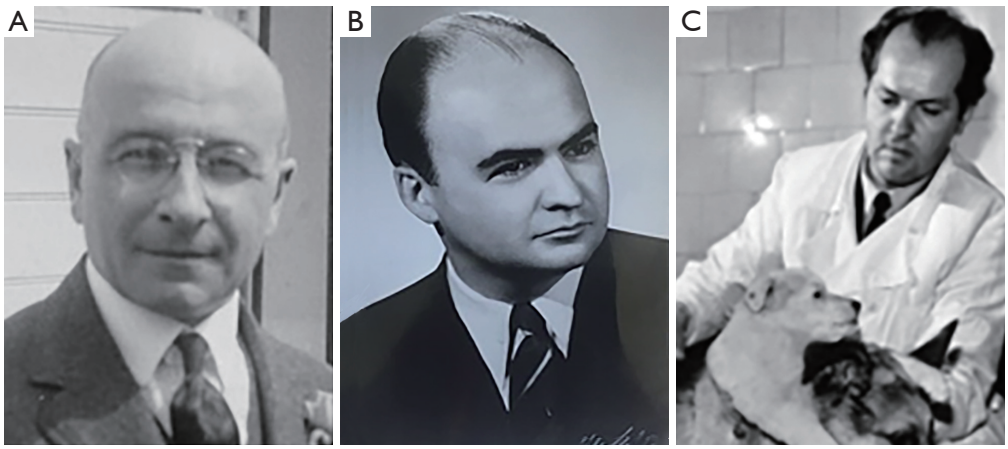


Figure 1 Pioneers of experimental lung transplantation. (A) Alexis Carrel MD, "1912 Nobel Prize in Physiology or Medicine". (B) Henri Metras MD. (C) Vladimir Demikhov MD.

Methods

A comprehensive search of the medical literature using Ovid and PubMed search engines was conducted for progression of all aspects of lung transplantation, including surgical techniques, immunosuppression progression, donor selection criteria evolution, recipient criteria evolution, new technology used to support the patient prior and after transplant, along with donor organ management and the Lung Allocation Scoring (LAS) system variables and their impact on outcomes after lung transplantation.

Animal models and technical feasibility phase

The first period includes the preclinical and laboratory phase, which was approximately six decades long (1900s to early 1960s). It was a period of hard work and commitment to configure the anatomy, physiology and best surgical techniques for lung transplantation. Based on his excellent work on blood vessel anastomosis and on organ reimplantation and transplantation, Alexis Carrel (*Figure 1*) was the first to report a lung transplant surgery when he performed an en-bloc heart and lung transplant to a cat in 1907 (2). In 1934, Alex Carrel, in collaboration with Charles Lindbergh, developed the first "functional pump oxygenator" (3).

Four decades after Carrel's first attempt, Vladimir Demikhov (*Figure 1*) was performing lung transplantations with animal models in his laboratory, including en-bloc heart and lungs and right lower lobe transplantation in dogs in 1946. In 1947, he was able to successfully perform two isolated lung transplants; however, survival was 1 and 4 weeks, respectively (4).

In 1950, Henri Metras (*Figure 1*) reported the first successful double-lung transplant in a dog. His surgical description included three major technical advances: the first bronchial artery anastomosis to the subclavian artery, main bronchial anastomosis, and a left atrium to pulmonary vein anastomosis; all these techniques are still being used (5).

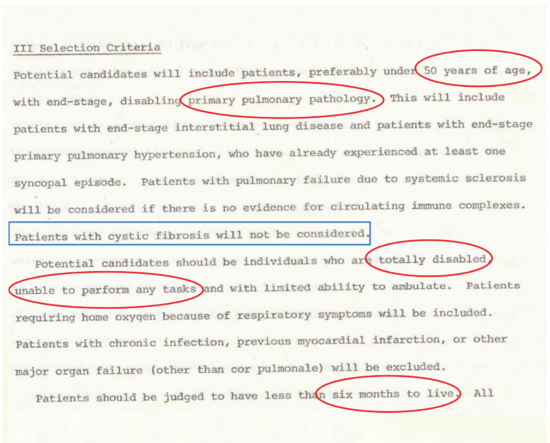
As part of the first period in lung transplantation, it is also worthwhile noting that Juvenelle *et al.* performed the first lung reimplantation, while studying the autonomic nerve supply in the lung for a potential treatment of asthma (6). It is also worthwhile mentioning that the concept and importance of immune rejection was still not well comprehended until 1944, when Medawar introduced it during his studies of skin graft rejection (7). This will be discussed in detail in immunosuppression section.

Major milestones in the second phase of human lung transplantation

The second period in lung transplantation started in 1963 when James Hardy (*Figure 2*) performed the first human lung transplantation. He implanted a left lung to a patient suffering from cancer. The patient survived the operation but died 18 days later due to renal failure (8). Four weeks later, Magovern and Yates reported the second human left lung transplant, which was another surgical success, but the patient only lived for 7 days (9).

Over the next 20 years only 44 lung transplants were performed and most of the patients died within the first

Figure 2 Dr. James Hardy, who performed the first human lung transplantation.


III Selection Criteria

Potential candidates will include patients, preferably under 50 years of age, with end-stage, disabling primary pulmonary pathology. This will include patients with end-stage interstitial lung disease and patients with end-stage primary pulmonary hypertension, who have already experienced at least one syncopal episode. Patients with pulmonary failure due to systemic sclerosis will be considered if there is no evidence for circulating immune complexes. Patients with cystic fibrosis will not be considered.

Potential candidates should be individuals who are totally disabled, unable to perform any tasks and with limited ability to ambulate. Patients requiring home oxygen because of respiratory symptoms will be included. Patients with chronic infection, previous myocardial infarction, or other major organ failure (other than cor pulmonale) will be excluded.

Patients should be judged to have less than six months to live. All

Figure 4 Toronto Lung Transplant Group selection criteria form, 1982.

Figure 3 Toronto Lung Transplant Group. From left to right: Griff Pearson MD, Tom Todd MD, Joel Cooper MD, and sitting, Alec Patterson MD.

month after operation; the longest survival of 10.5 months was reported by Derom *et al.* in 1968, but the patient spent most of that time in the hospital and ultimately died of chronic organ rejection (10).

Combined heart and lung transplant had the same rough start; when Denton Cooley performed the first human en-bloc heart and lung transplant in 1968, the patient survived for only 14 h, but it was considered as proof of concept because it showed that the procedure was feasible and could be successful (11). Five months later, Clarence Walton Lillehei reported the second combined heart-lung transplant, and the patient lived for 8 days (12).

Lung transplant reset, reboot and survival success

Driven by the success of cyclosporine in kidney and liver transplant, the Stanford team, led by Drs. Norman Shumway, Bruce Reitz, and John Wallwork, performed what is considered the first long-term successful heart and bilateral lung transplant in 1981 (13). In parallel the Toronto Lung Transplant Group led by Joel Cooper and Alexander Patterson (*Figures 3,4*) had also changed the immunosuppression protocol and in 1986 were able to perform the first successful long-term single-lung transplant for a pulmonary fibrosis patient, known as lung transplant #45, who lived for 7 years (14). Soon after, they reported a case of bilateral lung transplant in an emphysematous patient who lived for 16 years (15).

During this period, multiple other concepts in the field were challenged; at that time, bilateral lung transplantation was considered the only viable option for patients with emphysema, the rationale being that when a single-lung transplant was performed, the non-transplanted lung became hyperinflated, affecting the function of the transplanted lung. In 1989 this theory was challenged by Mal *et al.* who reported a single-lung transplant in a patient with emphysema without subsequent significant hyperinflation (16).

Driven by the success achieved from partial transplant of other organs, Starnes performed the first successful living-donor lobar lung transplantation (LDLLT) when

he replaced the right lung of a 12-year-old girl with her mother's right lower lobe, followed by bilateral lung transplant using two lower lobes of two different donors 1992 (17). It is worthwhile mentioning that the world's first lobar lung transplant was first attempted in Japan in 1966 by Shinoi *et al.* at Tokyo Medical College; the patient survived, but the transplanted lobe had to be removed on postoperative day 18 (18).

The concept of inverted lung transplantation was first described in a cadaveric lung transplantation by the Jean Paul Couetil and Alain Carpentier team in 1997 (19,20). However multiple nonstandard configurations of LDLLT as single-lobe transplants, native upper lobe sparing, inverted along with combine sparing and inverted lobes could be credited to Hiroshi Date and the Kyoto University team (21,22).

Other major surgical technical achievements

The technical aspects of both single- and double-lung transplants have evolved over the years. Advancement in lung transplantation was initially troublesome mainly due to the technical aspect of bronchial anastomosis. The poor healing of the bronchial anastomosis resulted in high morbidity and mortality rates due to anastomotic dehiscence. Initially, double-lung transplant was performed with an en-bloc approach with a single tracheal anastomosis. This technique had a high risk of tracheal dehiscence for which the anastomosis site was shifted to the level of the main stem bronchi. This technique was first described by Metras in 1950 (5), and later re-described by Noirclerc (23) and promoted by Cooper and Pasque in 1990 (24). Other techniques, such as telescoped bronchial anastomosis, were initially accepted due to the work of Veith *et al.* (25); this shifted towards end-to-end airway anastomosis when Garfein *et al.* proved it had less anastomotic stenosis and complication rates than telescoped bronchial anastomosis (26).

The lungs are the only solid organ that is transplanted without a systemic arterial blood supply. This peculiarity leads to several unique complications, including bronchial ischemia, granulation formation, mucosal sloughing, bronchial dehiscence, and bronchial stenosis. In order to reduce such complications, bronchial arterial revascularization (BAR) emerged as a technique to reduce the incidence of airway ischemia. It was first described in a human lung transplant by Haglin *et al.* (27) using the same technique that Metras described in 1950 on his animal models (5).

Since then, different techniques have been described for BAR, including greater saphenous vein conduit, internal mammary artery conduit, and donor aortic patch containing the origin of both bronchial arteries sewn directly to the recipient aorta (28-30). Even though BAR has been proven to be effective in decreasing bronchial anastomotic complications and has clinical advantages, including long-term survival, less infection rate and primary graft dysfunction (PGD), it is not widely used due to the technical challenges (31,32).

The surgical incision and the surgical approach have also evolved. Double-lung transplant used to be performed via sternotomy for a long period of time, but transitioned to a clamshell incision, which allows for better access to the posterior mediastinum for bronchial anastomosis. Although the clamshell technique was first described by Kortz in 1958 (33), it was not until 1990 that it was first reported being used for lung transplants (23,24). Due to healing complications, surgeons slowly shifted toward using a bilateral anterolateral thoracotomy, which allows excellent exposure without the need for sternal division.

Lung transplant and the rise of machines

Extracorporeal membrane oxygenation (ECMO) use in lung transplantation

As formerly mentioned, Alex Carrel and Charles Lindbergh developed the first "functional pump oxygenator" (3), which is considered to be the very first technology used for the development of the cardiopulmonary bypass (CPB) machine, ECMO, and *ex-vivo* support. The use of these later devices was a game changer in lung transplant surgery. Even though the first successful single-lung transplant and subsequent single-lung transplantations were usually performed without CPB (14), the en-bloc lung transplant used to be performed via a median sternotomy on CPB with tracheal anastomosis. The shift to bilateral sequential lung transplant with anastomosis at the level of the main bronchus showed the possibility to perform lung transplantation without CPB, especially in patients without pulmonary hypertension. This led to the pursuit of different ways to support the patient during the procedure and in the perioperative period with ECMO. ECMO is now used frequently in all steps of lung transplantation. Currently, there is sufficient data to favor the use of ECMO in patients with severe PGD (34,35). The progression in venovenous (VV) ECMO support and increased ECMO experience have led to better outcomes, along with increasing belief that better physical

condition of the patient before transplant will lead to better outcomes. These factors led to the use of VV ECMO bridge-to-transplant, giving patient time to be optimized and reconditioned while waiting for suitable lungs (36-38). Note that the first use of ECMO support as a bridge was in 1977 when Frank Vieth reported the use of VV ECMO as a bridge-to-transplant for 3 days, although the patient died after 10 days postoperative from a lung infection (39). Later, venoarterial (VA) ECMO was introduced to replace CPB as intraoperative support in patients who needed cardiac and pulmonary support. This was first reported in 2002 by Arpad Pereszlenyi (Vienna Group) who used it in a patient with pulmonary hypertension (40). The superiority of VA ECMO over CPB has been reported in multiple investigations since then (41,42).

Donation after cardiac death (DCD), ex-vivo lung perfusion (EVLP), and organ care system (OCS)

Even though the first human lung transplant used a DCD donor, almost all lung transplants performed in the following 30 years were done using brain-dead donors. This concept was driven by the need to increase the lung donor pool and was feasible because of the notion that lung tissue could remain viable for a few hours after cardiac death. It was proven by Egan *et al.* when they reported successful lung transplantations in animals using dead dogs' lungs up to 4 h after their death (43). Later, in 1995 Love *et al.* were able to replicate this success in humans by performing the first successful single-lung transplantation from a controlled DCD donor (44,45). The evolution and reliability of this technology is obvious when current data outcomes from DCD donors show no major difference in outcomes when compared with brain-dead donors (46,47).

The traditional method of transportation and preservation of lungs until the time of implantation is to keep them inside a cooler full of ice (outside cooling), aiming to keep temperature around 4 ℃; however, there is no way of verifying if the temperature remains stable during transportation, and another uncertainty is the temperature discrepancy between the outer surface of the lung and the inner lung tissue. Different techniques to overcome these have been attempted, such as using continuous perfusion of the lung (with cold perfusate) up to the time of transplant or what used to be called keeping the "heart and lungs alive" and functioning outside the body, which was suggested by Robicsek *et al.* (48,49). Using autoperfusion of the heart and lungs as a method of preservation to allow distant procurement was introduced in early 1980 by Robert Hardesty and Bartley Griffith (50). Using EVLP in DCD donors was introduced by Stig Steen and his team from Lund University in Sweden when they successfully performed a single-lung transplant from an uncontrolled DCD donor (Maastricht Categories I and II) using an EVLP support donor lung prior to transplant (51). This was a major accomplishment in lung transplantation, not only because it made DCD a safer option, but also helped increase the donor pool. The EVLP technology was enhanced and popularized by the Toronto Group, reporting similar survival rates when compared with conventional transplantation with similar physiologic and functional outcomes (52).

The use of EVLP has expanded the donor pool; according to the International Society of Heart and Lung Transplantation (ISHLT) registry, 20% of all DCD donors are transplanted after *ex-vivo* evaluation (53). EVLP also helps in the evaluation and reconditioning of marginal lungs, which has been proven and supported by multiple studies that have shown similar survival and PGD rates when compared with non-EVLP lungs. The use of EVLP has also made it possible to safely expand the time for implantation to more than just a few hours (54-56).

The EVLP system (*Figures 5*,*6*) provides a window of time to transport, evaluate and recondition the lungs outside the donor body prior to transplantation. In this case the lungs are transported on ice, then connected to the EVLP device to be evaluated and reconditioned in the donor hospital (57,58).

OCS (*Figure 7*) is a newer method of preserving, assessing and transporting lungs; the lungs are placed on OCS at the donor hospital, which allows the lungs to be preserved in warm physiologic conditions and ventilated during this time, while during transport and assessment the vascular resistance and airway pressures can be monitored. OCS minimizes the cold ischemia time and enables assessment and reconditioning of standard and borderline donor lungs, as proven by multiple studies using normal (INSPIRE trial) and extended donor criteria (EXPAND trial) (59-61). In 2019 OCS received FDA approval (62).

Immunosuppression and lung transplant

The current success of organ transplantation has been the result of research of investigators and scientists in many medical disciplines, but mainly by the exceptional work of pharmacists, immunologists, and hematologists. The immunosuppressive regimen chosen by Hardy *et al.* consisted

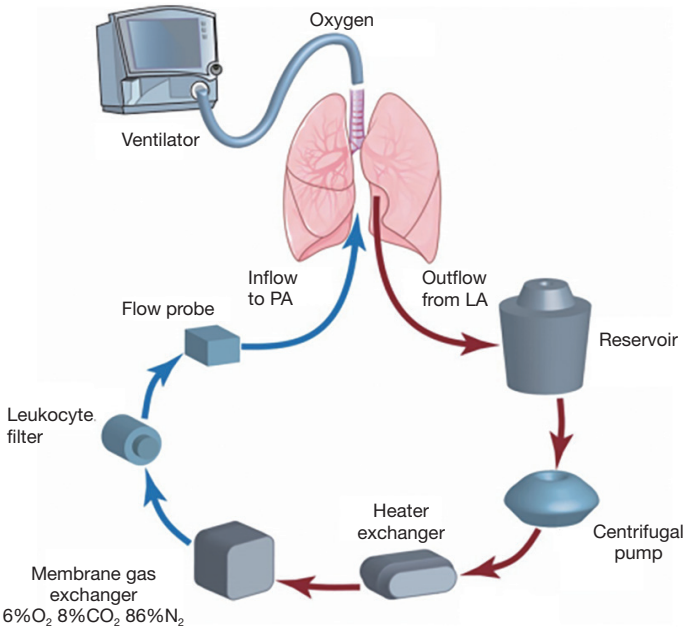


Figure 5 EVLP circuit with permission of Makdisi and Wozniak (57). EVLP, *ex-vivo* lung perfusion; PA, pulmonary artery; LA, left atrium.

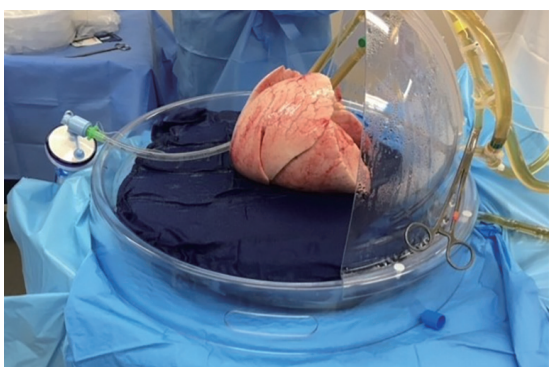


Figure 6 EVLP circuit [with permission of Makdisi *et al.* (58)]. EVLP, *ex-vivo* lung perfusion.

of preoperative thymic radiation with cobalt therapy directed to the mediastinum and postoperative immunosuppression with azathioprine and prednisone (8). Immunosuppression management during and after lung transplantation continues to develop, with more protocols and agents available for use, allowing for more individualization of immunosuppressive therapy. Immunosuppression in lung transplant, as with any organ transplant, consists of induction therapy to deplete the immune system in the immediate post-transplant period and to decrease the early interaction between the new lungs and the recipient immune system, and maintenance therapy to maintain long-term graft survival (there are different agents and different protocols that will be discussed in a different article in the series). Here we will discuss the major steps in the evolution of immunosuppression.

Although skin grafts have been used for hundreds of years, the concept and importance of immune rejection was still not well understood until 1944, when Peter Medawar (*Figure 1A)* introduced the concept from his studies of skin graft rejection (7). Corticosteroids have been a constant in immunosuppressive regimens since the beginning of solid organ transplantation, which Rupert Billingham found to prolong survival of skin homografts in rabbits (63). The first use of for corticosteroids in human solid organ transplant is credited to Hume *et al.* when they reported using corticosteroids in nine cases in the early 1960s (64); Willard Goodwin later reported using corticosteroids to reverse acute rejection in a living-donor kidney transplant recipient (65,66) and in 1963 Thomas Starzl, confirmed the efficacy of corticosteroids and the "almost miracle" effect (67).

Total body radiation used in the laboratory for solid organ transplant is often credited to William Dempster, who also treated dog homograft recipients with cortisone (68,69). However, Jean Hamburger (70) and René Küss (71) independently reported performing six successful transplants between 1959 and 1962 in non-twin recipients prepared by total body irradiation.

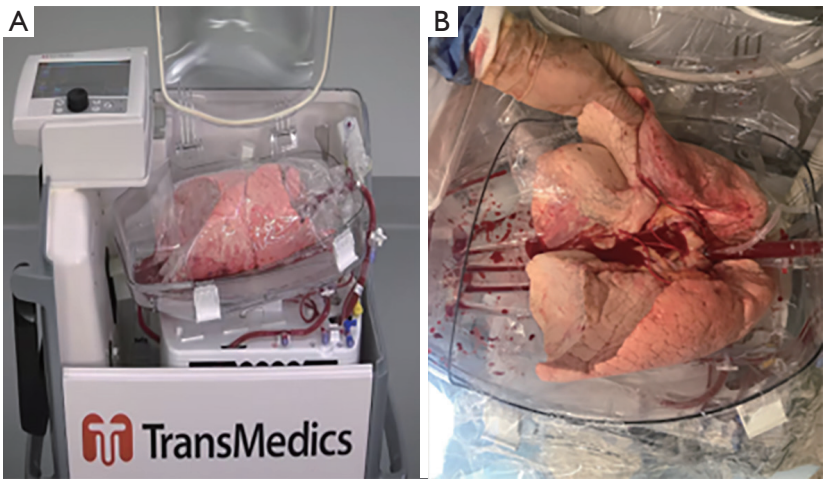


Figure 7 OCS lung. (A) Lungs under evaluation and reconditioning using OCS prior transplantation. (B) Lungs connected to OCS system prior evaluation process and transportation. OCS, organ care system.

In 1956 Gertrude Elion and George Hitchings, "1988 Nobel Prize winners in Physiology or Medicine", co-discovered and developed 6-mercaptopurine (6-MP) and azathioprine, both being purine analogs. Azathioprine is metabolized to 6-MP both *in vitro* and *in vivo* (72), and 6-MP was the first used in an animal transplant in 1959 when Schwartz and Dameshek demonstrated that 6-MP prolonged skin allograft survival in rabbits (73). This was the beginning of chemical immunosuppression in transplantation. Based on these studies, Zukoski *et al.* (74) and Calne (75) independently introduced 6-MP in their preclinical studies of a canine kidney transplant model. However, it was rapidly proven that azathioprine could prolong renal allograft survival when given with corticosteroids (76).

After it was shown in human kidney recipients that the addition of antilymphocyte globulin to azathioprine and prednisone improved treatment efficacy (77), Derom used this immunotherapy regimen for the patient who survived for 10 months in 1967 (10).

Cyclosporine was discovered in Norway in 1969 by Dr. Hans Peter Frey, and initially developed as a new antibiotic drug; however, its biological effects and the discovery of its immunosuppressive characteristics without major cytotoxicity by Drs. Thomas Starzl, Jean-François Borel and Hartmann Stähelin (78-80), led to the use of cyclosporine in a human transplant in 1978, when it was used for the first time in human kidney transplantation to treat post-transplant organ rejection (81). Inspired by the success of cyclosporine in kidney and liver transplant, in 1981 Stanford University gained US Food and Drug Administration (FDA) approval for the use of cyclosporine in clinical heart-lung transplantation, and the first successful transplant of the heart and both lungs was performed by Bruce Reitz and John Wallwork (13). This was in fact the first long-term success for any kind of lung transplant. Cyclosporine was approved by the FDA in 1983 and almost immediately Joel Cooper and the Toronto Lung Transplant Group changed their immunosuppression protocol to include cyclosporine and were able to perform the first successful long-term single-lung transplant in 1983 (14).

Tacrolimus (FK506) was originally discovered in 1984 and received FDA approval in 1994 (82,83). Trials revealed that patients treated with tacrolimus experienced significantly less acute rejection, and lymphocytic bronchitis was also less frequent among patients receiving tacrolimus compared with those receiving cyclosporine (84). Tacrolimus usage was found to be associated with a significantly reduced risk for bronchiolitis obliterans syndrome (BOS) grade ≥1 at 3 years when compared with cyclosporine, despite a similar rate of acute rejection. However, no survival advantage was detected (85-87). Currently, tacrolimus is the most popular calcineurin inhibitor in use, while mycophenolic acid is the dominant purine synthesis inhibitor used (88).

Since then, great progress has been made in developing immunosuppression regimens to prevent acute and chronic rejection of the lung allograft while also aiming to reduce the risk of opportunistic infection, a major side effect of immunosuppression. Early detection and treatment of graft dysfunction, infection, and chronic lung allograft dysfunction (CLAD) are essential for longer graft survival.

CLAD remains a major cause of morbidity and mortality following lung transplantation. BOS is the most common form of CLAD (65–75% of all CLAD cases) and restrictive allograft syndrome is the second most common form (89,90). Traditional diagnosis of BOS and CLAD used to be by pulmonary function test, bronchoalveolar lavage (BAL), transbronchial biopsy/conventional pathology, and radiologic findings (91,92). Although there is no treatment currently available to reverse CLAD after diagnosis, early identification allows proactive and targeted strategies to reverse the progression of the disease before irreversible allograft damage occurs (93,94). Nowadays, there are new revolutionary methods of early detection and diagnosis of CLAD using biomarkers via microarrays or RNA sequencing technology of samples collected from blood or BAL, including gene expression profiling, blood mRNA and miRNA transcriptome (95-97). For the future, genetic risk profiling of lung transplant recipients might be a promising approach to identifying patients at low risk of developing acute rejection and CLAD, which will probably lead to personalized immunosuppressive treatment with reduction of immunosuppressive treatment or the number of medical appointments, thus improving both health care efficacy, and quality of life (98).

Development of the organ donation and transplantation system in the USA

Organ transplantation requires collaboration among three different organizations: the donor hospital, the transplant center, and the organ procurement organization (OPO). Up until the mid-1970s, individual transplant centers and the local OPO used to manage all aspects of organ recovery. However, as there was no system to expand the availability of donor organs beyond the local OPO, the allocation was mainly restricted to only local patients. This resulted in transplant teams being unable to locate a compatible recipient in adequate time, leading to significant loss of good donor organs. In 1968, a scientific organization known as the Southeast Organ Procurement Foundation (SEOPF; now known as the American Foundation for Donation and Transplantation) was formed to enhance access to transplantation, improve quality and outcomes, and increase successful organ donation by facilitating collaboration between transplant centers and professionals, providing education, training, and sharing of best practices. In 1977, SEOPF implemented the first computer-based organ matching system, named UNOS (99,100).

With the promising outcomes of solid organ transplants, the number of transplant candidates and transplant centers were significantly increasing, so there was an urgent need of a nationwide system to collect data and coordinate organ allocation. In 1984, the US Congress passed the National Organ Transplant Act (NOTA) (PL 98-507) (101), which established the framework for an Organ Procurement and Transplantation Network (OPTN) to ensure the fair and efficient allocation of donor organs. It also resulted in the creation of the Scientific Registry of Transplant Recipients (SRTR) to evaluate the scientific and clinical status of patients' post-transplant. UNOS received a federal contract to operate both OPTN and SRTR to maximize the appropriate use of a deceased person's organs. The organizations role was also to establish a system to collect, store, analyze and publish data pertaining to the recipient waiting list, organ matching and transplants. In 1992, UNOS prepared the first-ever comprehensive report on transplant survival rates for all active US transplant centers (102). This data led to the establishing of objective outcome criteria, to assess and investigate underperforming transplant programs. Programs with lower-than-expected survival rates are then reviewed by a UNOS committee (103). In 2006, UNOS launched DonorNet, an internet-based system to notify transplant hospitals of newly donated organs for compatible candidates (99).

History of the donor LAS system

The development of the donor selection and matching system for lung allocation in the USA has been a complex, and at times, controversial process. The policy requirements instituted in the 1990s by OPTN was very simple: the donor lungs were allocated based on ABO match, the recipient residing within a 500-mile range of the donor organ/transplant center, and the amount of time that candidates had accrued on the waiting list in the local OPO. This basic system resulted in low numbers of lung transplantations and increasing numbers of deaths of eligible recipients on the waiting list, because it did not account for the recipient's severity of disease or prognosis, nor lung failure pathology. In 1995 OPTN recognized the clinical significance of idiopathic pulmonary fibrosis by giving it an extra 90-day credit on the waiting list compared with other pathological presentations (104).

In 2005 the OPTN changed the allocation system for lung transplantation in the USA by moving toward the LAS system for lung recipients, the score for which is calculated

from estimates of survival probability while on the lung transplant waiting list and following transplantation. Being a system intended to allocate lungs based on medical urgency and post-transplant survival, LAS is supposed to shorten the waiting time for very sick patients on the waiting list. In the years following implementation of the LAS system, wait-list times decreased, and the mean LAS of transplant recipients increased, consistent with a greater urgency for transplantation; the total number of patients transplanted also increased (105). In a retrospective study, Egan *et al.* compared the data of listed patients listed between the 5 years prior to LAS implementation [2000–2004] and the 5 years after [2006–2011] and as expected there was significant decrease in wait-list deaths from 500/year to 300/year, the distribution of recipient diagnoses also changed with significantly with more patients with fibrotic lung disease receiving transplants and the age of recipients also increased significantly (106).

Although the development of the system was complex and controversial it was quickly adopted by other countries system (107,108). In 2020 the USA implemented an update of the LAS to better cope with patients with pulmonary hypertension, and that was refined in 2021 (109-111).

Recipient selection evolution

The appropriate selection of lung transplant recipients is an important determinant of overall outcome and has experienced major evolution over the years. In the early days of lung transplantation, recipients were often ventilator-dependent, malnourished or had steroid-related myopathy and osteoporosis. The patient's candidacy used to be made by a few members of each transplant center without well-defined criteria, but with the surge in transplant volume, transplant institutions started to develop criteria for recipient's candidacy that were constantly modified. In the late 1980s and early 1990s, the important value of preoperative pulmonary rehabilitation and improved general physical condition was recognized, and currently most lung transplantation recipients are ambulatory. Wildevuur and Benfield (12) reviewed the first 23 human lung transplants performed by 20 surgeons, finding only one patient who survived more than 30 days. The majority of those patients presented with advanced cancer or were labeled as having terminal or preterminal conditions, conditions now considered absolute contraindication for transplant (112). In their research form for lung transplant application, the Toronto Lung Transplant Team in 1982 set well-defined recipient selection criteria (*Figure 4*), with lung recipient candidates preferably be under 50 years of age, with primary pathology of the lung (excluding cystic fibrosis), unable to perform tasks due to their condition, and judged to have less than 6 months of life expectancy. These patients were recruited as experimental transplant recipients. Those with chronic infection, history of previous myocardial infarction, or another major organ failure were excluded (113).

For some time thereafter, many practitioners considered single-lung transplantation to be inappropriate for patients with emphysema due to the assumption that there would be dynamic hyperinflation of the native lung after transplantation. However, that theory was disproven in 1989 when Mal *et al.* demonstrated the feasibility of single-lung transplant in patients with emphysema without contralateral hyperinflation (16).

In 1998, the American Society for Transplant Physicians, the American Thoracic Society, the European Respiratory Society and the ISHLT organized a committee of international experts to provide a consensus opinion regarding the appropriate timing of referral for transplantation and listing of candidates for lung transplantation. This was the first international consensus of lung transplantation candidate selection (114). The goal of these recommendations was to assist physicians in appropriately identifying patients who are the most likely to benefit from lung transplantation, though they were largely based on expert opinion rather than being evidence based. The pulmonary council of ISHLT took the lead and updated these guidelines in 2006 and 2014 (115,116) and will be discussed in a different article in this series.

Transplant team concept

The lung transplant procedure technically takes several hours between evaluation and transplantation. However, the transplant process itself is long, meticulous, and may take weeks or months to assess the patient's candidacy. In addition, post-transplant recovery can take months, even a year or more, as lung transplant recipients are vulnerable to many problems and need continuous adjustment of medications following transplant to prevent infection or organ rejection. Ensuring a good outcome requires a team built of healthcare professionals trained in multiple specialties working together to ensure favorable outcomes. The providers may include pharmacists, pulmonologists, surgeons, nutritionists, physical therapists, nurses, social workers, and transplant coordinators.

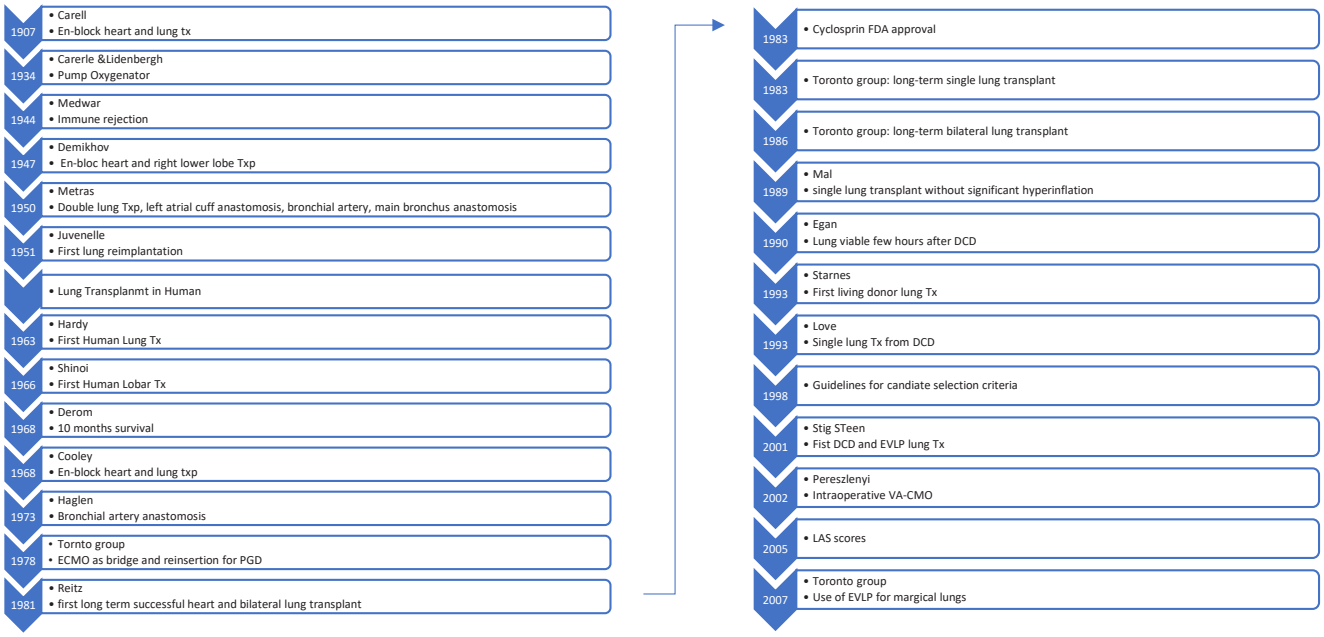


Figure 8 Landmarks of lung transplant history. DCD, donation after cardiac death; ECMO, extracorporeal membrane oxygenation; EVLP, *ex-vivo* lung perfusion; LAS, Lung Allocation Score; Tx, transplant.

Summary

It is an understatement to say that lung transplant had evolved tremendously in the past 60 years: surgical techniques have been improved, selection criteria have been modified, and new technologies had emerged to improve the quality of the donor lung. All of this, combined with the introduction of mechanical circulatory support, has resulted in a meaningful growth in lung transplantation and improved long-term survival. *Figure 8* is a good summary of the major landmarks of this evolution.

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