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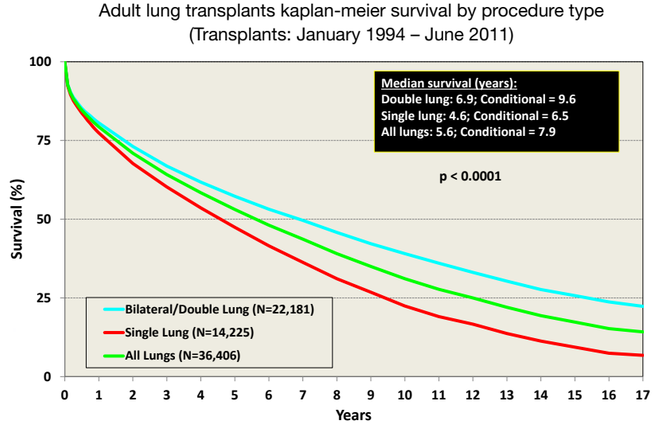
SPECIAL ISSUE: Heart-Lung Transplantation

Guest Editors: Don Hayes Jr, Bryan A. Whitson



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Editorial Correspondence

Daoyuan Wang, MD
Managing Editor
Pioneer Bioscience Publishing Company
Address: 9A Gold Shine Tower, 346-348 Queen's Road Central, Sheung Wan, Hong Kong. Tel: +852 3488 1279; Fax: +852 3488 1279.
Email: jtd@thepbpc.org
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Cover image:

Adult lung transplants Kaplan-Meier survival by procedure type (single or bilateral) from January 1994 to June 2011, modified with permission (See P1022 in this issue).

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Preface

Heart and lung disease (HLT) individually are major causes of morbidity and mortality worldwide. Due to physiological needs, disease in either organ may lead to failure of the other organ. The only accepted therapy for end-stage heart, lung, or heart-lung failure is organ transplantation.

Recent advances in technology for heart and lung support has resulted in mechanical devices, such as ventricular assist devices and extracorporeal life and organ support, are quickly becoming a component of routine care. The science of these devices and related technologies is just launching. The identification of appropriate patient populations and sufficient organs available for transplantation remain to be important limitations in optimal long-term clinical outcomes.

This issue of *Journal of Thoracic Disease* (*JTD*) provides in-depth analyses of the most current scientific data regarding the surgical management of heart, lung, and heart-lung failure and cardiothoracic transplantation. The discussion embraces both adult and pediatric populations and includes indications and selection criteria, surgical techniques, immunosuppression, and mechanical device support for the heart and lung.

This issue is dedicated to the worldwide effort to treat cardiopulmonary disease. The prevention and subsequent medical treatment of HLT is preferred and more ideal; however, advancement in therapeutic options for end-stage cardiopulmonary disease needs to continue in order to treat those patients unresponsive to standard care. A group of highly respected authors has produced an issue discussing current best practices and offer opportunities to continue expanding the treatment of cardiopulmonary failure.

Don Hayes Jr, MD, MS, MEd[1], Bryan A. Whitson, MD, PhD[2]

[1]Associate Professor of Pediatrics and Internal Medicine. Medical Director, Advanced Lung Disease Program. Medical Director, Lung and Heart-Lung Transplantation Programs, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio 43205, USA (Email: hayes.705@osu.edu.)

[2]Assistant Professor of Surgery. Surgical Director of the End-Stage Cardiopulmonary Failure Program. Co-Director COPPER Laboratory, Division of Cardiac Surgery, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA (Email: bryan.whitson@osumc.edu.)

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Review Article

Indications and outcomes in adult lung transplantation

Bryan A. Whitson[1], Don Hayes Jr[2,3,4]

[1]Department of Surgery, [2]Department of Pediatrics, [3]Department of Internal Medicine, The Ohio State University, Columbus, OH, USA; [4]Section of Pulmonary Medicine, Nationwide Children's Hospital, Columbus, OH, USA

Correspondence to: Don Hayes Jr, MD, MS. The Ohio State University, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA. Email: hayes.705@osu.edu.

Abstract: Lung transplantation (LTx) is a treatment option for end-stage lung disease that would be otherwise fatal for specific patient populations. The most common indications for LTx in adults remain to be chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. Recent trends include performing re-transplantation while more patients over the age of 65 years are undergoing LTx. Even with these tendencies, slight improvements in survival have occurred. This article briefly reviews recent developments in adults undergoing LTx.

Keywords: Adults; indications; outcomes; lung transplantation (LTx)

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Introduction

Lung transplantation (LTx) is the only therapeutic option for end-stage parenchymal lung diseases or pulmonary vascular disorders. In 1963, Hardy *et al.* (1) performed the first lung transplant in a 58-year-old male patient who died of nephrotoxicity. Since then, significant advancements have occurred regarding organ preservation, extracorporeal support of both donor organs and recipients, surgical techniques, immunosuppressive therapeutic agents, and allograft surveillance, along with the advent of multidisciplinary, collaborative medical and surgical teams to provide care to patients after LTx. The purpose of this brief review is to review indications for LTx in adult patients and to present clinical outcomes.

Recent trends in lung transplant numbers

The International Society for Heart and Lung Transplantation (ISHLT) Registry provides detailed annual information on patients who have undergone LTx. The most recent report in 2013 summarized data from 43,428 adult lung and 3,703 adult heart-lung transplant recipients and their donors through June 30, 2012 (2). The number of lung transplants has continued to rise, especially over the last 5 years (*Figure 1*); however, this increase in demand for organs has coincided with a reduction in number of available donor lungs (2,3). Coinciding with the increase in total lung transplants, patients who are older than 65 years undergoing LTx are on the rise (*Figure 1*) (2,3). Similarly, the age of donor lung allografts is on the rise (4).

Indications for lung transplantation (LTx) in adults

The decision to perform LTx is a complex treatment that carries considerable surgical risks. *Table 1* shows the indications for lung transplants in adults performed between January 1995 and June 2012, while *Figure 2* provides the major indications by year from 1990 to 2011 (2). Revision of international guidelines for lung transplant candidates was last published in 2006 by Orens *et al.* (5) with a revised update being published soon, which will include pediatric recommendations for the first time.

Table 2 lists the major disease categories that should be considered for LTx. Patients with these pulmonary disorders should be referred for consideration for LTx at any point if these characteristics exist or if the patient or primary healthcare provider has further questions regarding

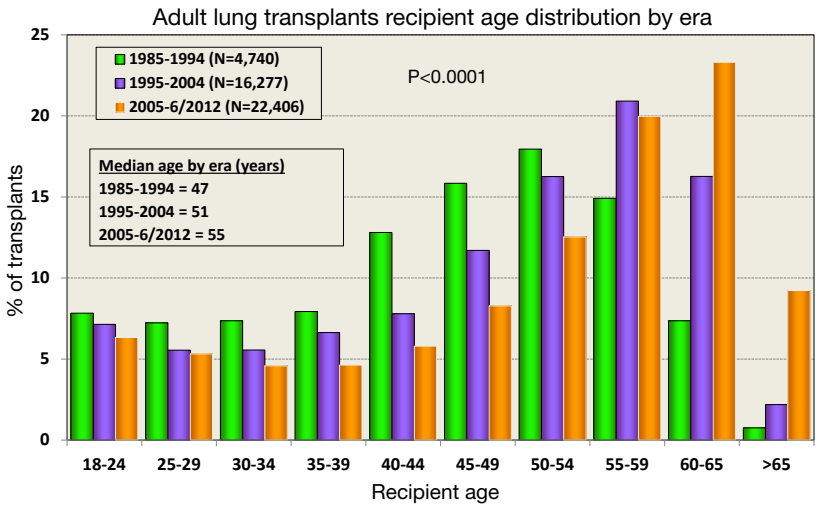

Figure 1 Major indications for lung transplants by year (%) from 1990 to 2011, modified with permission (2). The age distribution of lung transplant recipients was compared between eras using a chi-square test. A significant P value means that at least one of the groups is different than the others but it doesn't identify which group it is.

Table 1 Indications for adult lung transplants between January 1995 to June 2012, modified with permission (2)

Diagnosis	Single lung (N=14,197) No. (%)	Bilateral lung (N=23,384) No. (%)	Total (N=37,581) No. (%)
COPD* (without alpha-1 antitrypsin deficiency)	6,312 (44.5)	6,290 (26.9)	12,602 (33.5)
COPD* (with alpha-1 antitrypsin deficiency)	753 (5.3)	1,429 (6.1)	2,182 (5.8)
Interstitial lung disease (with idiopathic pulmonary fibrosis)	4,872 (34.3)	4,032 (17.2)	8,904 (23.7)
Bronchiectasis associated with cystic fibrosis	229 (1.6)	6,002 (25.7)	6,231 (16.6)
Idiopathic pulmonary arterial hypertension	87 (0.6)	1,073 (4.6)	1,160 (3.1)
Pulmonary fibrosis, other	563 (4.0)	820 (3.5)	1,383 (3.7)
Bronchiectasis	59 (0.4)	956 (4.1)	1,015 (2.7)
Retransplant (obliterative bronchiolitis)	276 (1.9)	292 (1.2)	568 (1.5)
Retransplant (not obliterative bronchiolitis)	182 (1.3)	220 (0.9)	402 (1.1)
Sarcoidosis	265 (1.9)	689 (2.9)	954 (2.5)
Connective tissue disease	156 (1.1)	332 (1.4)	488 (1.3)
Obliterative bronchiolitis (not retransplant)	98 (0.7)	298 (1.3)	396 (1.1)
Lymphangioleiomyomatosis	136 (1.0)	255 (1.1)	391 (1.0)
Congenital heart disease	56 (0.4)	269 (1.2)	325 (0.9)
Cancer	7 (0.0)	29 (0.1)	36 (0.1)
Other	146 (1.0)	398 (1.7)	544 (1.4)

*, COPD, chronic obstructive pulmonary disease.

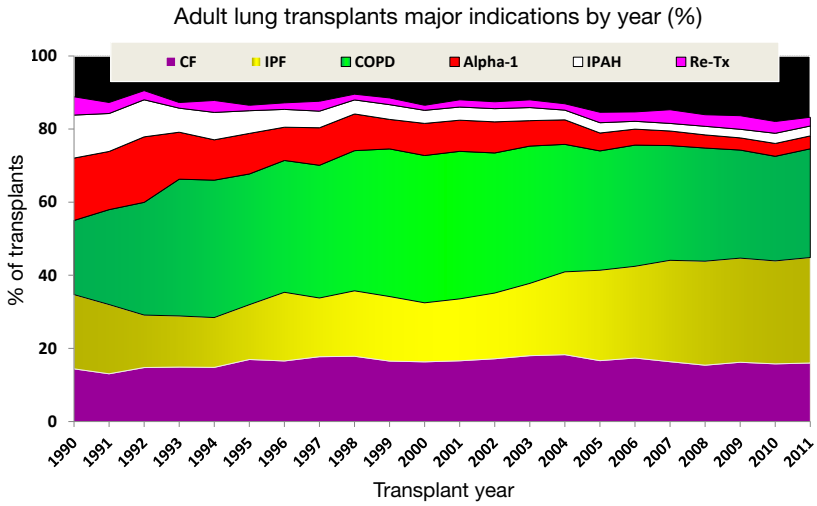

Figure 2 Adult lung transplants recipient age distribution by era from 1985 to 2012, modified with permission (2).

Table 2 Indications for lung transplantation according to underlying major diseases
Chronic obstructive pulmonary disease (with or without alpha-1 antitrypsin deficiency)
BODE (body-mass index, airflow obstruction, dyspnea, and exercise) index >5
FEV_1 <20% of predicted
Diffusion capacity <20% of predicted
Pulmonary hypertension or cor pulmonale despite oxygen therapy
Hypercapnia, P_aCO_2 >50 mmHg
Fibrotic lung disease
Histologic or radiographic evidence suggestive of usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP)
FVC <60% of predicted
Diffusion capacity <39% of predicted (UIP) or <35% of predicted (NSIP)
Drop in FVC by ≥10% or diffusion capacity by ≥15% over a 6-month period
Drop in S_aO_2 on pulse oximetry by <88% on 6-minute walk test
High-resolution CT imaging with honeycombing (fibrosis score >2)
Pulmonary hypertension
Cystic fibrosis
FEV_1 <30% of predicted
P_aO_2 <55 mmHg
P_aCO_2 >50 mmHg
Exacerbations requiring intensive care unit stay
Increasing frequent of pulmonary exacerbations requiring antibiotic therapy
Recurrent and/or refractory pneumothorax
Recurrent hemoptysis not controlled by bronchial artery embolization
Pulmonary hypertension
Progressive weight loss, body mass index <18 kg/m^2
Idiopathic pulmonary arterial hypertension
Low or declining 6-minute walk test at <380
Maximum oxygen intake <10.4 mL/min/kg
World Health Organization functional stage III or IV on maximal medical therapy
Cardiac index <2 L/min/m^2
Right atrial pressure >15 mmHg
Failure of intravenous epoprostenol therapy or equivalent

BODE, body-mass index, airflow obstruction, dyspnea, and exercise; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 3 Absolute contraindications for lung transplantation
Malignancy in the last 2 years except for cutaneous squamous and basal cell tumors, 5-year disease-free interval is prudent
Dysfunction of another major organ system (heart, liver, or kidney) that is not amenable to treatment
Noncurable xtrapulmonary infection (active viral hepatitis B, hepatitis C, human immunodeficiency virus)
Significant chest wall/spinal deformity
Nonadherence and/or inability to follow through with medical therapy or office follow-up
Untreatable psychiatric or psychologic condition(s) associated with the inability to cooperate or comply with medical therapy
Lack of dependable social support system
Substance addiction (alcohol, tobacco, or narcotics) within the last 6 months

Table 4 Relative contraindications for lung transplantation
Age older than 65 years
Critical or unstable clinical condition
Severely limited functional status with poor rehabilitation potential
Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria
Severe obesity defined as a body mass index (BMI) exceeding 30 kg/m^2
Severe or symptomatic osteoporosis
Mechanical ventilation
Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux should be optimally treated before transplantation

the potential benefit of LTx. *Tables 3*,*4* outlines both absolute and relative contraindications for LTx as recently recommended. In short, LTx should not be considered in a patient with a florid infection, recent malignant tumor, continued addictive behavior, or lacks reliable social support. Infectious issues are different in cystic fibrosis with controversy continuing with most centers generally not offering transplant in patients colonized with *Burkholderia cenocepacia* and extreme caution used in offering transplant in the presence of *Mycobacterium abscessus*. Relative contraindications are determined by the individual centers with updated recommendations under development to be soon available.

Clinical outcomes

Survival after LTx in adult patients has slowly improved over the last 30 years (2). One contributing factor is the increasing number of bilateral lung transplants being performed, especially in the younger patient population (*Figure 3*). The improvement in survival has improved in a stepwise fashion as outlined in *Figure 4*.

Innovations

Hardy *et al.* were clearly innovative in 1963 when they performed the first lung transplant. Novel discoveries continue to influence the outcomes of patients with advanced lung disease regarding LTx. The use of extracorporeal support has made an immediate impact as it is commonplace for patients to be bridged to LTx with extracorporeal membrane oxygenation (ECMO) (6-16), but ECMO remains to be a relative contraindication in the current published guidelines, thus the need for an update. The use of ECMO as a means to bridge was recently reported with similar outcomes as lung retransplantation (6). A major innovation with the advent of normothermic ex vivo lung perfusion by the group at the University of Toronto has resulted in the successful transplantation of donor lungs that would have been previously discarded (17,18). This technology uses extracorporeal means to support donor organs. More recently, induction immunosuppression was shown to have a significantly positive effect on survival (19). Discoveries continue to include modifications of currently available treatments as best practice still continues to evolve in LTx.

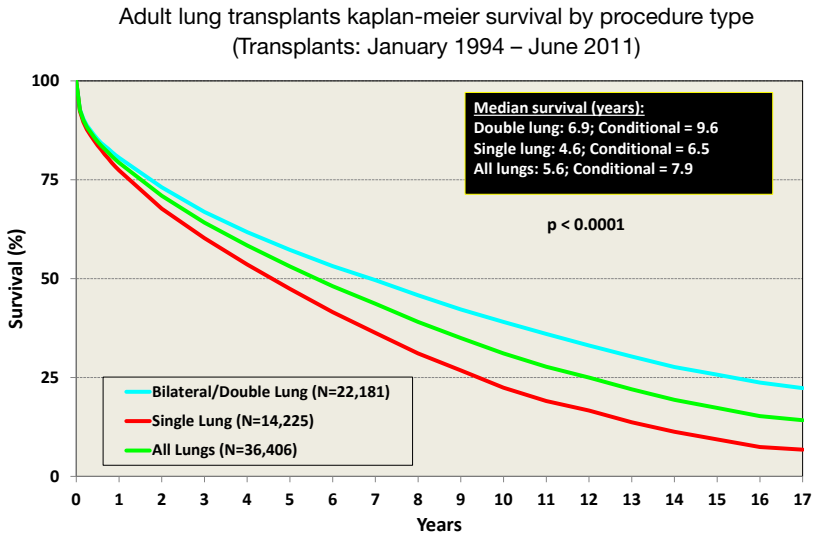

Figure 3 Adult lung transplants Kaplan-Meier survival by procedure type (single or bilateral) from January 1994 to June 2011, modified with permission (2). Survival was calculated using the Kaplan-Meier method, which incorporates information from all transplants for whom any follow-up has been provided. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. The median survival is the estimated time point at which 50% of all of the recipients have died. The conditional median survival is the estimated time point at which 50% of the recipients who survive to at least 1 year have died. Because the decline in survival is greatest during the first year following transplantation, the conditional survival provides a more realistic expectation of survival time for recipients who survive the early post-transplant period. Survival rates were compared using the log-rank test statistic.

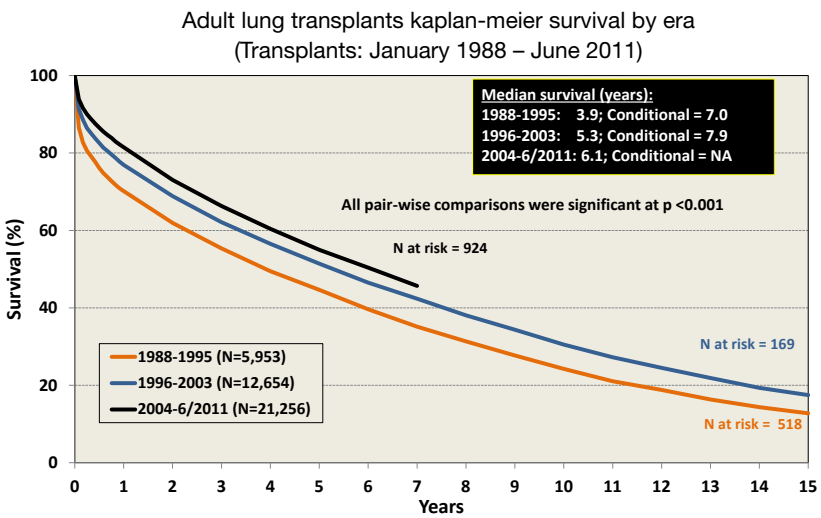

Figure 4 Adult lung transplants Kaplan-Meier survival by era from January 1988 to June 2011, modified with permission (2). Survival was calculated using the Kaplan-Meier method, which incorporates information from all transplants for whom any follow-up has been provided. Since many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact rates because the time of death is not known for all patients. The median survival is the estimated time point at which 50% of all of the recipients have died. The conditional median survival is the estimated time point at which 50% of the recipients who survive to at least 1 year have died. Because the decline in survival is greatest during the first year following transplantation, the conditional survival provides a more realistic expectation of survival time for recipients who survive the early post-transplant period. Survival rates were compared using the log-rank test statistic. Adjustments for multiple comparisons were done using Scheffe's method.

Conclusions

Based on the recent advancements, the future is very bright in the care of patients with advanced lung disease who require LTx. Despite recent novel discoveries and innovations, further work is needed to improve and enhance not only the current technologies and treatments, but how we use them and in what clinical situation. Multi-center studies are badly needed in order to even further improve outcomes in LTx.

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References

1. Hardy JD, Webb WR, Dalton ML Jr, et al. Lung homotransplantation in man. JAMA 1963;186:1065-74.
2. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
3. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients. OPTN/SRTR 2010 Annual Data Report, 2011 [May 17, 2014]. Available online: http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx
4. Abecassis M, Bridges ND, Clancy CJ, et al. Solid-organ transplantation in older adults: current status and future research. Am J Transplant 2012;12:2608-22.
5. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55.
6. Hayes D Jr, Higgins RS, Kilic A, et al. Extracorporeal Membrane Oxygenation and Retransplantation in Lung Transplantation: An Analysis of the UNOS Registry. Lung 2014;192:571-6.
7. Fischer S, Simon AR, Welte T, et al. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. J Thorac Cardiovasc Surg 2006;131:719-23.
8. Ricci D, Boffini M, Del Sorbo L, et al. The use of CO2 removal devices in patients awaiting lung transplantation: an initial experience. Transplant Proc 2010;42:1255-8.
9. Haneya A, Philipp A, Mueller T, et al. Extracorporeal circulatory systems as a bridge to lung transplantation at remote transplant centers. Ann Thorac Surg 2011;91:250-5.
10. Hämmäinen P, Schersten H, Lemström K, et al. Usefulness of extracorporeal membrane oxygenation as a bridge to lung transplantation: a descriptive study. J Heart Lung Transplant 2011;30:103-7.
11. Bermudez CA, Rocha RV, Zaldonis D, et al. Extracorporeal membrane oxygenation as a bridge to lung transplant: midterm outcomes. Ann Thorac Surg 2011;92:1226-31; discussion 1231-2.
12. Hayes D Jr, Kukreja J, Tobias JD, et al. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. J Cyst Fibros 2012;11:40-5.
13. Bittner HB, Lehmann S, Rastan A, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery. Ann Thorac Surg 2012;94:942-9; author reply 949-50.
14. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763-8.
15. Lang G, Taghavi S, Aigner C, et al. Primary lung transplantation after bridge with extracorporeal membrane oxygenation: a plea for a shift in our paradigms for indications. Transplantation 2012;93:729-36.
16. Hoopes CW, Kukreja J, Golden J, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013;145:862-7; discussion 867-8.
17. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364:1431-40.
18. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg 2012;144:1200-6.
19. Whitson BA, Lehman A, Wehr A, et al. To induce or not to induce: a 21st century evaluation of lung transplant immunosuppression's effect on survival. Clin Transplant 2014;28:450-61.

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Review Article

Pediatric lung transplantation: indications and outcomes

Stephen Kirkby, Don Hayes Jr

Section of Pulmonary Medicine, Lung and Heart-Lung Transplant Program, Nationwide Children's Hospital and The Ohio State University, Columbus, OH, USA

Correspondence to: Stephen Kirkby, MD. Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA.
Email: stephen.kirkby@nationwidechildrens.org.

Abstract: Lung transplantation (LTx) is a treatment option for infants and children with untreatable and otherwise fatal pulmonary diseases. To date, over 1,800 lung transplants have been performed, most frequently in children over the age of five years. The most common indications for transplantation in children overall are cystic fibrosis (CF) and idiopathic pulmonary hypertension (PH). The surfactant protein deficiencies, other interstitial lung diseases (ILDs), and congenital heart disease are important indications among young children and infants. Re-transplantation is an option for selected recipients with chronic allograft rejection. Overall survival following pediatric LTx is similar to that encountered in adult patients, with recent registry data indicating a median survival of 4.9 years. Other outcomes such as the incidence of bronchiolitis obliterans (BO) and the presence of key post-transplant co-morbid conditions are also similar to the experience in adult lung transplant recipients.

Keywords: Lung transplantation (LTx); pediatrics; infants; indications; survival

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Introduction

Lung transplantation (LTx) is a therapeutic option for children and infants with incurable and end-stage diseases of the lungs or pulmonary vascular system. While LTx in this special age group carries unique challenges, there is ample evidence to suggest that outcomes are similar to those in adults. Pediatric LTx offers the potential for prolonging life expectancy and also improving quality-of- life. The purpose of this paper is to review the most common indications for LTx in pediatric patients and to present available outcomes data for children undergoing this procedure.

The era of LTx began over 50 years ago when Hardy and colleagues performed the first transplant in 1963 in a 58 year-old man with bronchial carcinoma (1). Since that time, significant progress in the field has been made in regards to surgical technique, immunosuppressive regimens, recognition and treatment of allograft rejection, and the development of multidisciplinary and collaborative surgical and medical teams to provide optimal long-term care (2-5). Over 43,000 LTx have been performed in adults with the most common indications being COPD, pulmonary fibrosis and cystic fibrosis (CF) (6).

The first pediatric LTx involved a 16 year-old boy with familial pulmonary fibrosis and was performed in 1987 at the University of Toronto (4). Successful LTx has subsequently been performed in children of all ages, including infants, yet the majority of pediatric cases involve children over the age of 11. The most recent registry data of the International Society for Heart and Lung Transplantation (ISHLT) reports that 1,875 lung transplantations have been performed in pediatric patients, most commonly for a diagnosis of CF (7). There is clear evidence that survival after pediatric LTx has improved in recent years, a trend most reflective of improvement in early survival (8). As the total volume of pediatric transplants is far exceeded by those performed in adults, it is not surprising that the total number of centers providing LTx in children and infants is small. In 2011, only 43 centers reported LTx in children with the majority being located in North America and Europe. In addition, most pediatric centers have very low volumes compared to adult programs, with only one center performing more

Table 1 Most common indication for pediatric lung transplantation. Data adapted from 2012 ISHLT registry report (7)

Age group	Indication for transplant	Total transplants in age group (%)
11-17 years	CF	71
	IPAH	8
	Re-transplant	5
6-10 years	CF	53
	IPAH	9
	BO (non-retransplant)	7
	Retransplant	6
	IPF	6
1-5 years	IPAH	22
	IPF	17
	Pulmonary fibrosis (other)	9
	Retransplant	9
<1 year infants	Surfactant protein b deficiency	17
	Congenital heart disease	17
	IPAH	13

CF, cystic fibrosis; IPAH, idiopathic pulmonary arterial hypertension; BO, bronchiolitis obliterans; IPF, idiopathic pulmonary fibrosis.

than 10 transplants per year. The total number of children undergoing LTx each year has been slightly greater than 100 from 2006-2011.

There are several important anatomical, physiological, psychosocial and epidemiological factors that are indeed unique to LTx in children and infants (2,4,9,10). First, the size of both pediatric lung donor and recipient may present special surgical challenges with regards to size matching and bronchial and vascular anastomoses. The immune systems of children, and infants in particular, are immature and developing and therefore unlike those of adults. It has been suggested that young children may have less risk of acute and chronic allograft rejection and therefore have more tolerance of transplantation (11). There is also evidence that certain infectious issues, particularly seasonal respiratory tract viruses, are of paramount importance in pediatric LTx (12,13). Nutrition, gastroesophageal reflux disease, and risk of aspiration may all have direct influence on morbidity and survival in children (14). Another important factor in successful LTx in pediatric patients is appropriate parental support to provide for the very complex post-transplant care. Unreliable psychosocial circumstances can in fact be a major obstacle to long term success (15). Adolescents in particular may struggle with adherence to prescribed therapies as the mature and gain more independence. Taken together, these special considerations in pediatric LTx are important factors to consider in evaluating a potential patient for transplant candidacy.

Indications for pediatric lung transplantation (LTx)

CF is the most common indication for LTx in pediatric patients overall and was the primary diagnosis in 1,063 of 1,875 (57%) children in the IHSLT registry (5). Idiopathic pulmonary arterial hypertension (IPAH) is the second most-common indication for LTx, and 164 cases (9%) have been reported. Other less common but important indications for pediatric LTx include: idiopathic pulmonary fibrosis (IPF), surfactant protein deficiencies and other diseases now more uniformly classified as childhood interstitial lung diseases (chILD), congenital heart disease, and re-transplantation.

There is substantial variability in the indication for LTx among sub-groups of pediatric patients divided by age. For instance, in older children and adolescents aged 11-17 years, CF is the indication for LTx in 70% of cases. However CF becomes less predominant in younger aged patients, representing 53% of LTx in children 6-10 years of age and less than 5% in young children under age 5. The most common indication for LTx among children age 1-5 and 6-10 years of age is IPAH. Congenital heart disease, the chILD syndromes including surfactant protein B deficiency (SP-B), and IPAH are the most common indication for infant LTx. The most common indications for pediatric LTx categorized by age group are demonstrated in *Table 1*.

Cystic fibrosis (CF)

CF is the most common fatal genetic disease affecting Caucasian populations worldwide. This disease is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel responsible for ion transport across epithelial cells lining the respiratory tract. Abnormal CFTR results in dehydration of the airways, thick mucus, and poor mucociliary clearance. This causes a cycle of obstruction of the airways by viscous mucus, chronic airway infection, and chronic lung and systemic inflammation. Chronic respiratory failure from CF lung disease is the most

common cause of death (16,17). The hallmarks of treatment are airway clearance via chest physiotherapy, aerosolized medications that can help rehydrate and reduce mucus viscosity, anti-inflammatory therapies, aggressive treatment of both chronic and acute on chronic infections, and optimization of key CF comorbidities such as malnutrition and diabetes mellitus (16,18). More recently developed genotype-specific therapies may help correct the underlying CFTR defect which causes CF (19). Survival for CF has improved dramatically over the last several decades with the most recent median survival exceeding 41 years (20). However, despite improvements in treatment and improved survival, LTx remains an important treatment option for advanced CF lung disease in childhood and adolescence. CF is the most common reason for transplant in pediatrics and CF is the third most common indication among adults.

Idiopathic pulmonary arterial hypertension (IPAH)

IPAH is the second most-common indication for LTx in pediatric patients overall, and is the most common indication among children aged 1-5 years. Pulmonary hypertension (PH), in general, is defined by a mean pulmonary artery pressure at rest greater than 25 mm Hg and a pulmonary vascular greater than 3 Woods after three months of age (21). Recent classification strategies by the World Health Organization and the Pediatric Task Force of the 5th World Symposium convening in Nice, France [2013] have further grouped patients with PH into several main categories by main mechanism of elevation in pulmonary artery pressure (22). A detailed description of the classification schema of PH is beyond the scope of this paper, but Group 1 (pulmonary arterial hypertension) diseases which include IPAH, heritable PAH, and PAH associated with congenital heart diseases are the most frequently encountered entities causing end-stage cardiopulmonary disease in pediatric patients.

The natural history of untreated IPAH is one of rapid clinical deterioration and frequent death, often within three years of initial diagnosis. The progression of children with PH may be more rapid than in adult patients (23-25). However, in recent years the development of more effective pulmonary vasodilator medications, in particular the prostacyclin based therapies, has demonstrated clear improvements in survival (21). Despite the benefits of IPAH medications, the ultimate outcome in most pediatric patients is death and therefore LTx remains an important and viable treatment strategy (26). Current guidelines in adults would suggest referral for LTx when patients reach New York Heart Association functional classification of level III to IV, meaning patients who are symptomatic with exertion or at rest. The applicability of these subjective categories in young children may be of limited utility, however there is evidence that children with supra-systemic right heart pressures and those who experienced hemoptysis were at increased risk for death on the waitlist (26). This would suggest that children with IPAH and these poor prognosticating features should be listed early for transplantation.

Interstitial lung disease (ILD) and surfactant protein deficiencies

It has been well-recognized that ILD in pediatric patients differs significantly from that in adults (27). The chILD syndromes have been described as a heterogeneous group of disorders affecting children less than 2 years old with respiratory signs and symptoms (most frequently tachypnea), impairment in gas exchange (hypoxemia) and evidence of diffuse parenchymal lung disease on chest imaging. The American Thoracic Society has recently published clinical guidelines for the diagnosis and management of these patients (28). The chILD syndromes can be sub-divided as those syndromes affecting infants and those not specific to infancy.

The surfactant protein deficiencies are quite rare diseases but are the most common indication among the chILD diseases for LTx in infancy. There have been four surfactant protein deficiency syndromes described including SP-B, surfactant protein C deficiency (SP-C), adenosine triphosphate binding cassette protein member A3 (ABCA3), and thyroid transcription factor (*NKX2.1* gene) (29-31). The presentation of the surfactant deficiencies may vary from severe hypoxemic respiratory failure in the newborn period (32) (typical of SP-B) to a more insidious development of tachypnea, hypoxemia and diffuse interstitial changes on chest imaging later in infancy (more typical of SP-C) (33). Diagnosis of these syndromes can be achieved through genetic sequencing technology (28). Perhaps the most important (and most aggressive) surfactant protein deficiency is SP-B, which is recognized as a universally fatal disease and LTx is considered the only viable treatment option (34).

Other important chILD syndromes that may lead to LTx in infants include disorders of lung development such as alveolar capillary dysplasia with misalignment of pulmonary veins (a disease affecting infants in the newborn period that is believed to be uniformly fatal) and growth abnormalities

such as neonatal chronic lung disease (bronchopulmonary dysplasia) (35).

BO and re-transplantation

BO refers to obstructive lung disease resulting from bronchiolar inflammation and is described pathologically by circumferential peribronchial fibrosis that can constrict or completely obliterate the lumen of the bronchiole (36). BO can be caused by infectious or non-infectious insults to the airways which trigger the process of inflammation and fibrosis. Post-infectious BO in children is frequently associated with severe viral (adenovirus) or mycoplasma infections (37). Non-infectious BO can occur in children as a consequence of autoimmune diseases, inhalational injuries, and Stevens-Johnson syndrome among others. However, a very important cause of BO is post-transplant in nature. BO can occur as a consequence of pediatric bone marrow transplantation (38,39). Any of these specific etiologies of BO can ultimately manifest in respiratory failure and be an appropriate indication for LTx in children.

The most common group of patients with BO undergoing consideration for LTx is in fact primary lung recipients who develop chronic allograft dysfunction over time. BO remains the major obstacle to long term success in LTx recipients and current treatment options are limited (40). Therefore BO following initial LTx remains an important indication for consideration of re-transplantation. Pediatric patients may be given special consideration for re-transplantation, as achieving an expected graft survival and therefore "good outcome" defined by some standards may not allow a child to reach adulthood. The indications for pediatric lung re-transplant can generally be classified as those patients with chronic allograft dysfunction with BO versus those without BO who suffer graft failure from other causes. A total of 118 pediatric lung re-transplants have been reported, and available data suggests this procedure is most beneficial in patients with chronic graft failure occurring greater than 1 year post-initial transplant (28,41).

Outcomes

Although the most common indications for LTx in pediatric patients differ from those of adults with end-stage lung disease, the available data on outcomes suggest that the success of LTx is quite similar. While survival is certainly the paramount outcome measure for LTx recipients of all ages, other variables such as the incidence of graft rejection, the frequency of key comorbid conditions, the need for re-transplantation, and overall quality of life and functional status are also clinically important.

Survival data

The annual IHSLT Registry report is the most comprehensive database of thoracic LTx performed worldwide (28). Participation in this registry is voluntary but it is believed that this data encompasses the vast majority of pediatric LTx performed each year. In 2011, a total of 43 centers performed LTx in pediatric patients with the vast majority of these centers located in Europe (n=20) and North America (n=18). The 2013 ISHLT registry data of pediatric LTx performed between 1990 and 2011 reports a median survival of 4.9 years for pediatric patients. This observed survival is statistically similar to that of adult LTx recipients (4.9 versus 5.4 years, P=0.3459, *Figure 1*) Like in adults, there has been a clear improvement in survival when comparing era of transplant, with median survival of 3.3 years among those transplanted between 1988-1999 versus median survival of 5.8 years in those transplanted in the modern era of 2000-2011 (P≤0.001). Pediatric patients with CF have similar survival to those without CF, with median survival of 4.7 years in both groups (*Figure 2*). While it appears children age 6-10 years may have improved early survival, there is no clear difference in overall long term survival (*Figure 3*). The 2012 US Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/STRS) data analysis of pediatric LTx performed in the US in 2007-2008 reported post-transplant survival of 96.3% at 30 days, 87% at one year, 60.1% at 3 years, and 49% at 5 years (42).

The most common cause of death in the first 30 days following pediatric LTx is graft failure which accounts for approximately 30% of early mortality (7). Non-CMV infection and graft failure are the most common causes of death from one month to one year post transplant, and account for over 50% of mortality in this time period. Bronchiolitis obliterans syndrome (BOS), like in adults, is the most common cause of death after the first year following pediatric LTx, and represents 40% of deaths at both 1-3 and 3-5 years post-transplant. BOS is responsible for 47% of deaths after 5 years (28). Thus BOS remains the biggest obstacle to long-term survival in both pediatric and adult LTx recipients. This data is consistent with that presented in the OPTN/STRS database (42).

The available data on re-transplants in pediatric

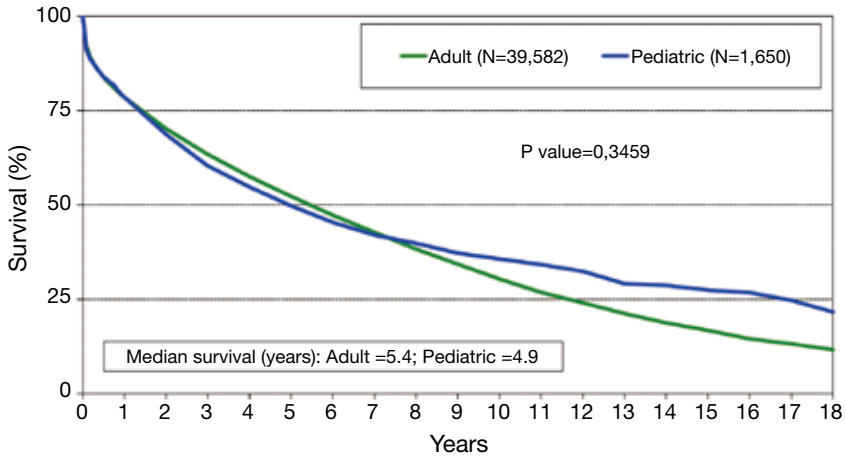

Figure 1 Median survival in pediatric lung transplant recipients compared to adults (7).

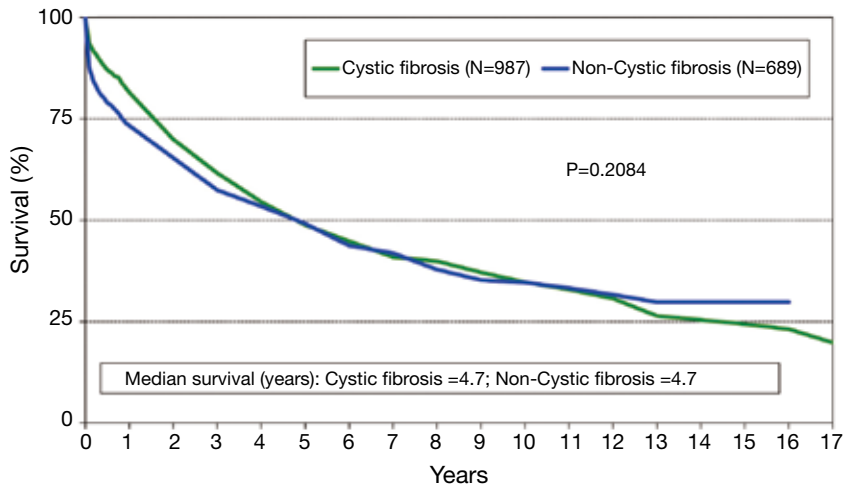

Figure 2 Median survival in pediatric lung transplant recipients with CF versus non-CF (7).

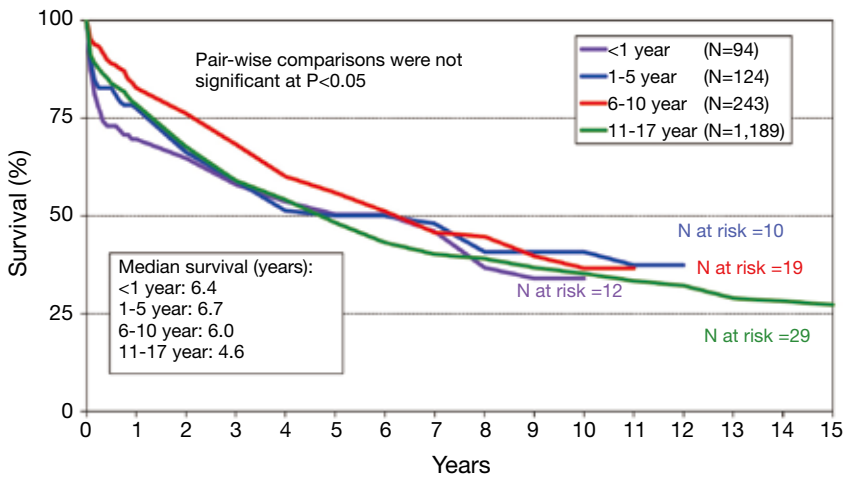

Figure 3 Median survival in pediatric lung transplant recipients by specific age group (7).

patients suggest that outcomes are worse compared to the initial transplant. There were 118 pediatric re-transplants performed between 1994 and 2012, and the approximately 23% of these procedures were performed within 12 months of the original. Three year survival among re-transplants is significantly lower than that of primary transplants (58% *vs.* 45%, P=0.026.) There was no significant difference between indications for re-transplant when comparing BOS to non-BOS related cases (28). It appears that the best outcomes for pediatric lung re-transplant are achieved in patients that are further than one year removed from initial transplant and are not ventilator dependent (41).

There are multiple studies that highlight survival characteristics and special considerations among specific groups of pediatric LTx recipients. A controversial study regarding the benefit of LTx for children with CF, published by Liou and colleagues, analyzed data from the CF Foundation and United Network for Organ Sharing databases between the years 1992 and 2002 (43). This group concluded that few children with CF achieved an overall survival benefit from LTx. Since that time, a large analysis of adult data from 2005-2009 (the lung allocation score era) demonstrated a strong improvement in adults with CF undergoing LTx (44). Many pediatric LTx centers and leading experts in the field have cited several reasons why the data from Liou at al may not be applicable to individual children with CF in the current era of LTx, citing the transition to the current lung allocation system in the US as well as controversies regarding the statistical analysis and cohort used in the study among others (45,46). There is no clear evidence that the frequency of pediatric LTx for CF has decreased in recent years, although with advances in the care of CF patients it is reasonable to anticipate a future shift towards more transplantations occurring in adulthood as opposed to childhood or adolescence. Over the past decade, it has become clear that CF patients with chronic infection with *Burkholderia cenocepacia* infection are particularly at risk for poor outcomes following LTx, primarily due to infection in the post-transplant period (47,48). Therefore, infection with *B. cenocepacia* is considered a contraindication at most centers.

Among diseases other than CF, there is data to suggest equivalent post-transplant survival. For instance, a retrospective single center review of 26 children undergoing LTx for IPAH showed a median survival of 5.8 years and 1- and 5-year survival of 95% and 61% respectively (26). Likewise, a multicenter retrospective chart review of 31 children undergoing LTx for diffuse lung disease (encompassing the chILD syndromes) showed comparable survival compared to children undergoing LTx for other indications (49).

The most common indications for LTx in infants are SP-B deficiency, congenital heart disease, and IPAH. Successful LTx in infants may be particularly challenging due to factors such as donor availability, size of the donor and recipient, risk of post-transplant respiratory viral infection, and other physiological factors such as aspiration risk. Infant LTx is a very rare procedure performed only at a handful of centers. In 2011 only four infant transplants were performed in the US, a number far below the number of heart transplants performed in this age group (42). An analysis of the UNOS database reported similar overall survival among 80 infants (<1 year of age) compared to older children and adolescents (age 1-18 years). This study also suggested an improved conditional survival for those infants surviving at least 1 year (50). This data suggests a potential protective advantage of the immature immune system of infants, and is corroborated by a previous study demonstrating a decreased incidence of allograft rejection among infants (11).

Outcomes other than survival

There appears to be a similar incidence of key post-transplant comorbid conditions following LTx in both pediatric and adult populations. The most commonly encountered co-morbidities at one year following LTx in pediatrics include hypertension, renal dysfunction, hyperlipidemia, and diabetes mellitus. These same conditions increase in frequency in survivors at 5 years post-transplant (7).

It may be challenging to assess functional status and quality of life in pediatric patients who may not be able to express their feelings adequately, and secondary reports from parents or physicians may be confounded by bias. However, the ISHLT registry did report that more than 80% of pediatric LTx recipients were given favorable assessments of functional status as measured by reported Lansky scores (7).

Summary

Pediatric LTx is a viable treatment option for infants and children with end-stage pulmonary diseases. The most common indications for children are CF and IPAH, while the chILD syndromes and congenital heart disease are the predominant indication for infants. Overall survival after LTx in the pediatric population is similar to the expected

survival in adults. Chronic allograft rejection remains the biggest obstacle to more prolonged survival, and re-transplantation in select patients may be a reasonable treatment option.

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References

1. Hardy JD, Webb WR, Dalton ML, et al. Lung Homotransplantation in Man. JAMA 1963;186:1065-74.
2. Sweet SC. Pediatric lung transplantation. Proc Am Thorac Soc 2009;6:122-7.
3. Kotloff RM, Thabut G. Lung transplantation. Am J Respir Crit Care Med 2011;184:159-71.
4. Mendeloff EN. The history of pediatric heart and lung transplantation. Pediatr transplant 2002;6:270-9.
5. Huddleston CB, Bloch JB, Sweet SC, et al. Lung transplantation in children. Ann surg 2002;236:270-6.
6. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
7. Benden C, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official pediatric lung and heart-lung transplantation report--2013; focus theme: age. J Heart Lung Transplant 2013;32:989-97.
8. Zafar F, Heinle JS, Schecter MG, et al. Two decades of pediatric lung transplant in the United States: have we improved? J Thorac Cardiovasc Surg 2011;141:828-32, 832.e1.
9. Huddleston CB. Surgical complications of lung transplantation in children. Semin Thorac Cardiovasc Surg 1996;8:296-304.
10. Huddleston CB. Pediatric lung transplantation. Curr Treat Options Cardiovasc Med 2011;13:68-78.
11. Ibrahim JE, Sweet SC, Flippin M, et al. Rejection is reduced in thoracic organ recipients when transplanted in the first year of life. J Heart Lung Transplant 2002;21:311-8.
12. Liu M, Worley S, Arrigain S, et al. Respiratory viral infections within one year after pediatric lung transplant. Transpl Infect Dis 2009;11:304-12.
13. Liu M, Mallory GB, Schecter MG, et al. Long-term impact of respiratory viral infection after pediatric lung transplantation. Pediatr Transplant 2010;14:431-6.
14. Benden C, Aurora P, Curry J, et al. High prevalence of gastroesophageal reflux in children after lung transplantation. Pediatr Pulmonol 2005;40:68-71.
15. Devine KA, Reed-Knight B, Loiselle KA, et al. Predictors of long-term health-related quality of life in adolescent solid organ transplant recipients. J Pediatr Psychol 2011;36:891-901.
16. Davis PB. Cystic fibrosis since 1938. Am J Respir Crit Care Med 2006;173:475-82.
17. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N Engl J Med 2005;352:1992-2001.
18. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003;168:918-51.
19. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663-72.
20. Cystic Fibrosis Foundation Patient Registry, 2012 Annual Data Report Bethesda, Maryland©2013 Cystic Fibrosis Foundation. Available online: http://www.cff.org/livingwithcf/qualityimprovement/patientregistryreport/
21. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62:D117-26.
22. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-54.
23. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009;95:312-7.
24. Barst RJ, McGoon MD, Elliott CG, et al. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113-22.
25. Barst RJ, Ertel SI, Beghetti M, et al. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011;37:665-77.
26. Goldstein BS, Sweet SC, Mao J, et al. Lung transplantation in children with idiopathic pulmonary arterial hypertension: an 18-year experience. J Heart Lung Transplant 2011;30:1148-52.
27. Hamvas A, Deterding R, Balch WE, et al. Diffuse lung disease in children: Summary of a scientific conference. Pediatr Pulmonol 2014;49:400-9.
28. Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline:

classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med 2013;188:376-94.
29. Wert SE, Whitsett JA, Nogee LM. Genetic disorders of surfactant dysfunction. Pediatr Dev Pathol 2009;12:253-74.
30. Whitsett JA. Genetic disorders of surfactant homeostasis. Paediatr Respir Rev 2006;7 Suppl 1:S240-2.
31. Shulenin S, Nogee LM, Annilo T, et al. ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med 2004;350:1296-303.
32. Nogee LM, Garnier G, Dietz HC, et al. A mutation in the surfactant protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. J Clin Invest 1994;93:1860-3.
33. Nogee LM, Dunbar AE 3rd, Wert S, et al. Mutations in the surfactant protein C gene associated with interstitial lung disease. Chest 2002;121:20S-21S.
34. Palomar LM, Nogee LM, Sweet SC, et al. Long-term outcomes after infant lung transplantation for surfactant protein B deficiency related to other causes of respiratory failure. J Pediatr 2006;149:548-53.
35. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. Am J Respir Crit Care Med 2011;184:172-9.
36. Mauad T, Dolhnikoff M. Histology of childhood bronchiolitis obliterans. Pediatr Pulmonol 2002;33:466-74.
37. Fischer GB, Sarria EE, Mattiello R, et al. Post infectious bronchiolitis obliterans in children. Paediatr Respir Rev 2010;11:233-9.
38. Nishio N, Yagasaki H, Takahashi Y, et al. Late-onset non-infectious pulmonary complications following allogeneic hematopoietic stem cell transplantation in children. Bone Marrow Transplant 2009;44:303-8.
39. Uhlving HH, Buchvald F, Heilmann CJ, et al. Bronchiolitis obliterans after allo-SCT: clinical criteria and treatment options. Bone Marrow Transplant 2012;47:1020-9.
40. Snell GI, Paraskeva M, Westall GP. Managing bronchiolitis obliterans syndrome (BOS) and chronic lung allograft dysfunction (CLAD) in children: what does the future hold? Paediatr Drugs 2013;15:281-9.
41. Scully BB, Zafar F, Schecter MG, et al. Lung retransplantation in children: appropriate when selectively applied. Ann Thorac Surg 2011;91:574-9.
42. Valapour M, Paulson K, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: Lung. Am J Transplant 2013;13:149-77.
43. Liou TG, Adler FR, Cox DR, et al. Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 2007;357:2143-52.
44. Thabut G, Christie JD, Mal H, et al. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. Am J Respir Crit Care Med 2013;187:1335-40.
45. Sweet SC, Aurora P, Benden C, et al. Lung transplantation and survival in children with cystic fibrosis: solid statistics--flawed interpretation. Pediatr Transplant 2008;12:129-36.
46. Adler FR, Aurora P, Barker DH, et al. Lung transplantation for cystic fibrosis. Proc Am Thorac Soc 2009;6:619-33.
47. Aris RM, Routh JC, LiPuma JJ, et al. Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type. Am J Respir Crit Care Med 2001;164:2102-6.
48. De Soyza A, McDowell A, Archer L, et al. Burkholderia cepacia complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. Lancet 2001;358:1780-1.
49. Rama JA, Fan LL, Faro A, et al. Lung transplantation for childhood diffuse lung disease. Pediatr Pulmonol 2013;48:490-6.
50. Khan MS, Heinle JS, Samayoa AX, et al. Is lung transplantation survival better in infants? Analysis of over 80 infants. J Heart Lung Transplant 2013;32:44-9.

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Review Article

Lung donor selection criteria

John Chaney[1], Yoshikazu Suzuki[2], Edward Cantu III[2], Victor van Berkel[1]

[1]Department of Cardiothoracic Surgery, University of Louisville School of Medicine, Louisville, KY, USA; [2]Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Correspondence to: Victor van Berkel, MD, PhD. Department of Cardiothoracic Surgery, University of Louisville School of Medicine, 201 Abraham Flexner Way, Suite 1200, Louisville, KY 40202, USA. Email: victor.vanberkel@louisville.edu.

Abstract: The criteria that define acceptable physiologic and social parameters for lung donation have remained constant since their empiric determination in the 1980s. These criteria include a donor age between 25-40, a arterial partial pressure of oxygen (PaO_2)/FiO_2 ratio greater than 350, no smoking history, a clear chest X-ray, clean bronchoscopy, and a minimal ischemic time. Due to the paucity of organ donors, and the increasing number of patients requiring lung transplant, finding a donor that meets all of these criteria is quite rare. As such, many transplants have been performed where the donor does not meet these stringent criteria. Over the last decade, numerous reports have been published examining the effects of individual acceptance criteria on lung transplant survival and graft function. These studies suggest that there is little impact of the historical criteria on either short or long term outcomes. For age, donors should be within 18 to 64 years old. Gender may relay benefit to all female recipients especially in male to female transplants, although results are mixed in these studies. Race matched donor/recipients have improved outcomes and African American donors convey worse prognosis. Smoking donors may decrease recipient survival post transplant, but provide a life saving opportunity for recipients that may otherwise remain on the transplant waiting list. No specific gram stain or bronchoscopic findings are reflected in recipient outcomes. Chest radiographs are a poor indicator of lung donor function and should not adversely affect organ usage aside for concerns over malignancy. Ischemic time greater than six hours has no documented adverse effects on recipient mortality and should not limit donor retrieval distances. Brain dead donors and deceased donors have equivalent prognosis. Initial PaO_2/FiO_2 ratios less than 300 should not dissuade donor organ usage, although recruitment techniques should be implemented with intent to transplant.

Keywords: Lung transplant; donor criteria; review

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Introduction

Lung transplantation is an established therapy for selected patients with end-stage pulmonary disease. Since the first successful lung transplant in 1983 by Dr. Joel Cooper and his team, over 42,000 recipients have benefitted from this procedure worldwide. Advances in surgical techniques, postoperative care, and immunosuppression therapy have led to improved short- and long-term survival following lung transplantation. Despite this success, the number of suitable lung donors remains a significant limitation. Today many donors are judged based on empiric criteria developed in the 1980s (See *Table 1*) (2,3).

Most centers agree that these criteria are too strict and use extended criteria donors (ECD) that do not completely meet the traditional empiric criteria (4). Many centers advocate use of ECD to effectively increase the donor pool with similar transplant outcomes (2,5-10). There is considerable variation in practice patterns among these centers and no uniformly accepted discriminating metric (6).

In-hospital mortality for lung transplantation is higher than for other solid organs. A significant contributor to this early hazard is primary graft dysfunction (PGD) (11). PGD occurs in up to 25% of recipients with associated 30 days

Table 1 Ideal lung donor criteria (1)	
Age	20-45
PaO_2:FiO_2	>350
Smoking history	None
Chest X-ray	Clear
Ventilation days	<5
Microbiology	Gram stain negative
Bronchoscopy	Clear
Ischemic time	<4 hours

mortality of 40-50%; compared to 5-10% without PGD (12). Accumulating evidence suggests that PGD is the end result of a series of injuries occurring in the donor lung from the time of brain death to reperfusion in the recipient (13). Therefore, concern over PGD may drive concern over lung donors, and thus limit the number of organs considered usable for transplant. Given the increasing burden of lung disease, the extremely limited number of suitable lung donors, and increasing waitlist mortality, it is not surprising that an increasing numbers of ECDs are being used. In the era of the lung allocation score, with preferential allocation to sicker recipients, it becomes more important to understand not only which ideal criteria can be ignored, but also in which context. Here, we break down donor criteria by individual factors and examine their effect on outcomes.

Age

Over the last 30 years, the average age of donors accepted for transplant has steadily increased. Retrospective cohort analysis of OPTN data revealed no increases in one year graft failure with donors aged 18-64. Ages <18 and >64 were associated with increased failure rates at one year but were not associated with increased PGD (14). Retrospective review of UNOS data from 2000-2010 confirms an increase in 1- and 3-year mortality for donors over the age of 65 without increases in bronchiolitis obliterans syndrome (BOS) (15). Further stratification into age groups [50-54, 55-59 and 60-64] did not reveal differences in one year mortality or FEV_1 (16). Available literature favors consistent outcomes for donors within the range of 18-64 years.

Gender

Donor and recipient gender combinations have been analyzed with mixed results. Fessart *et al.* failed to discern a difference in recipient survival after analysis of all gender combinations (17). Another single center retrospective study demonstrated an increase in survival and decrease in BOS for donor recipient gender mismatches (M→F and F→M). Male donor to male recipients specifically had a significant decrease in survival (18). International Society of Heart and Lung Transplant (ISHLT) registry review from 1995-2002 reflected a decreased survival in female donors to male recipients. Female donor to female recipient demonstrated a short and long term survival benefit (19). These results coincided with a multicenter study in France (20). The exact gender interactions between donor and recipient have yet to be defined to accurately shape our practice of transplant selection. There are questionable effects of hormones and size mismatch that have yet to be delineated in the literature.

Race

Retrospective review of lung transplants from 1997 to 2007 of race matched donors and recipients conferred a 3.3% decreased risk adjusted mortality at five years and 12% overall mortality in recipients with cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF) and single lung transplant (SLT). No changes in one year rejection rates were associated with race matching. Donor African American lungs reflected an increased risk of death regardless of recipient. Overall, specific recipient race was not associated with survival variability (21).

Smoking history

In the UK, a smoking history in donor lungs is associated with decreased recipient survival as compared to non-smoker donor lungs. The recipient survival, however, remains greater than that of the wait list population (22). This raises the argument that patients with high mortality risk would benefit from transplantation rather than succumb to illness on the waiting list. The interpretation of this data is also limited given recipients of smoker lungs were riskier candidates prior to surgery. Smoker donor lungs confer a higher risk of grade 3 PGD (23). A retrospective review of UNOS data on 766 heavy smoker donor lungs (>20 pack year history) revealed no increases in BOS or median survival (24). An additional single retrospective study of smoking donors revealed a worse early survival but no effect on long term survival and BOS incidence (25). This was confirmed by an additional retrospective single institution study that had

prolonged postoperative intubation and ICU stay in smokers but equivalent survival at three years (26). The overall findings coincide with an initial higher postoperative risk, and equivalent to higher long term recipient mortality risk, for smoker donor lungs as compared to non-smoker donor lungs. The mortality of patients receiving smoker donor lungs does reflect a lower mortality risk than that of patients on the transplant waiting list.

Bronchoscopic findings and cultures

Post transplantation pneumonia and sepsis are serious concerns to the transplant surgeon and previous guidelines for chest X-ray and bronchoscopy attempt to avoid transmission to immunosuppressed recipients. Gram stain evaluation of airways in a single center retrospective study found 12% of donors with a positive gram stain subsequently developed recipient pneumonia while 20% of negative gram stain donors went on to develop pneumonia. This refutes the association of donor gram stain with recipient pneumonia. In this study, however, donor lungs were not accepted if there was evidence of frank aspiration on bronchoscopy (27). Prospective analysis of donor airway cultures and bronchial tissue cultures revealed a <1.5% transmission rate of donor organ contamination (28). The lack of infection transmission from donor to non-suppurative based recipients is also been confirmed by two separate studies (29,30). With appropriate antibiotic prophylaxis to cover Pseudomonas and Staph aureus, risk of transmission of donor associated infection is negligible.

Radiographic findings

Donors undergo multiple radiographs prior to surgery. The high degree of interpretation variability have diminished the role in donor selection criteria (31). One third of possible donor radiographs in a retrospective survey had infiltrates, of which greater than half improved or spontaneously resolved. Improvement in infiltrates did not impact transplantation rates and led to unnecessary rejection. All patients transplanted in this study with positive infiltrates were alive at one year follow-up (32). No studies were found that correlated chest radiograph findings to recipient infections. The literature on radiographic donor exclusion is extremely limited, and the topic warrants further investigation.

Size mismatch

A recent review by Barnard published in 2013 thoroughly outlines size criteria for donor/recipient, and their results are briefly summarized here (33). Total lung capacity (TLC), recipient pathology (obstructive *vs.* restrictive), and height all factor in to appropriate matches. For double lung transplants, patients with emphysema should be matched to a donor with a 67-100% of the recipient's TLC. No definitive data is available for SLT for emphysema. For pulmonary hypertension and CF patients, the predicted total lung capacity (pTLC) of the donor may safely reach 120% of the recipient actual TLC. Due to the limitations in TLC that occur in pulmonary fibrosis, the recommendation for donors pTLC is to be within 20% of the halfway point between the recipients actual TLC and pTLC. For SLT for fibrotics, the donor pTLC should be within 20% of the recipient's pTLC. Little data exists for transplantation in overt size mismatch, but some suggest it is preferable to slightly oversize if possible and not undersize less than 80% (34).

Ischemic time and donor distance

Retrospective review of UNOS data of 6,055 transplants revealed no increased incidence of BOS or three years mortality in recipients with local, regional or national lung donors despite national ischemic times of (342±90) minutes (35). Additional single center studies verify no change in survival for ischemia greater than six hours (36-40). Donor ischemia time >7 hours and donor age >50 years compounded, however, was associated with decreased recipient survival at two years (41).

Donation after cardiac death

After evaluating the literature for effects of ischemia on recipient outcomes, the question of donation after cardiac death (DCD) use as opposed to beating heart brain dead donors inevitably follows. The largest single center study with 409 DCD lungs revealed a decrease in graft survival that did not reach statistical significance. The patient survival and BOS were comparable (42). Smaller, single center studies reveal either similar survival rates (43,44), or a modest decrement in survival (45). A single institutional study out of Madrid revealed PGD in 72%, Survival rates of 51% at five years, and BOS of 45% at five years (46). Use

of DCD donor lungs revealed a 100% survival at almost a year in eight patients (47). In total, these studies suggest the benefit of using DCD donors as a means to expand the available donor pool.

High risk donors

The Centers for Disease Control and Prevention (CDC) label high risk donors as those with exposure to HIV, prison inmates, IV drug users, prostitution history, high risk sexual history, and hemophiliacs. Limited data is available for lung transplantation in CDC high risk donors. Review of UNOS database on CDC high risk donors demonstrated equivalent one year mortality, postoperative infection, stroke and dialysis with normal donors. Around 9% of lung donors were classified as high risk and risk of disease transmission was less than 1%. Interestingly 95% of recipients surveyed would accept an organ from a high risk donor with an expected donor pool expansion of 10% (48).

Oxygenation

Arterial partial pressure of oxygen (PaO_2) is a traditional way to measure lung function. Donors with initial PaO_2/FiO_2 of <300, that improved to >300 with recruitment maneuvers, used in Australia were not associated with a decreased 30 days, 1, 2, 3 yrs survival or recipient PaO_2/FiO_2 ratio (8). High dose steroid administration after brain death was associated with an increase in PaO_2/FiO_2 of 16 +/-14 and a decrease of 34.2 +/-14 if steroids were not given. The outcome of recipients receiving steroid treated donor lungs was not analyzed in this study (49). Most importantly, UNOS data from 2000 to 2009 of 12,045 transplants failed to demonstrate a PaO_2 association with decreased survival, even with a PaO_2 of less than 200 in 1,830 patients (50). This may be due to preoperative gasses that are lower on initial reported PaO_2 and significantly improve after recruitment maneuvers, which are not consistently captured in the database.

Ex vivo lung perfusion (EVLP)

EVLP is an emerging technique used to evaluate and potentially salvage high-risk donor organs typically not suitable for lung transplantation (51). Steen initially utilized this technique to evaluate a DCD donor (52) and their success has sparked several studies around the world (51,53-57). These studies have demonstrated similar length of mechanical ventilation, rate of PGD, length of stay and mortality. How this technology will be implemented in allocation has yet to be determined despite the considerable promise they imply. Despite these challenges, it appears that the future of lung transplantation will capitalize on EVLP to safely expand the donor pool by expanding the limits of what defines a suitable donor.

Conclusions

There is little data to suggest that any of the historical criteria for defining the ideal lung transplant donor impact either short or long term outcomes. For age, donors should be within 18 to 64 years old. Gender may relay benefit to all female recipients especially in male to female transplants. Negative outcomes are associated with female donors to male recipients. Race matched donor/recipients have improved outcomes and African American donors convey worse prognosis. Smoking donors may decrease recipient survival post transplant, but provide a life saving opportunity for recipients that may otherwise remain on the transplant waiting list. No specific gram stain or bronchoscopic findings are reflected in recipient outcomes. Chest radiographs are a poor indicator of lung donor function and should not adversely affect organ usage aside for concerns over malignancy. Ischemic time greater than six hours has no documented adverse effects on recipient mortality and should not limit donor retrieval distances. Brain dead donors and deceased donors have equivalent prognosis. Initial PaO_2/FiO_2 ratios less than 300 should not dissuade donor organ usage, although recruitment techniques should be implemented with intent to transplant.

Although there have been multiple trials on individual lung donor criteria that fail to show negative recipient prognosis (58), there are few studies that evaluate the effects of multiple extended criteria compounded together in one donor lung. These compromises in physiology may have untold effects on PGD and overall patient mortality. In additional to donor selection, it is imperative to consider the recipient's pathology as a major harbinger of overall transplantation outcome (59). It is currently our recommendation that any single criteria outside of the historical ideals can safely be ignored, but we caution that the cumulative effects of multiple extended donation criteria in one donor have not been studied.

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References

1. Botha P, Rostron AJ, Fisher AJ, et al. Current strategies in donor selection and management. Semin Thorac Cardiovasc Surg 2008;20:143-51.
2. Filosso PL, Turello D, Cavallo A, et al. Lung donors selection criteria: a review. J Cardiovasc Surg (Torino) 2006;47:361-6.
3. Bhorade SM, Vigneswaran W, McCabe MA, et al. Liberalization of donor criteria may expand the donor pool without adverse consequence in lung transplantation. J Heart Lung Transplant 2000;19:1199-204.
4. Reyes KG, Mason DP, Thuita L, et al. Guidelines for donor lung selection: time for revision? Ann Thorac Surg 2010;89:1756-64; discussion 1764-5.
5. Botha P, Trivedi D, Weir CJ, et al. Extended donor criteria in lung transplantation: impact on organ allocation. J Thorac Cardiovasc Surg 2006;131:1154-60.
6. Meers C, Van Raemdonck D, Verleden GM, et al. The number of lung transplants can be safely doubled using extended criteria donors; a single-center review. Transpl Int 2010;23:628-35.
7. Pierre AF, Sekine Y, Hutcheon MA, et al. Marginal donor lungs: a reassessment. J Thorac Cardiovasc Surg 2002;123:421-7; discussion, 427-8.
8. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. Am J Respir Crit Care Med 1999;160:265-71.
9. Lardinois D, Banysch M, Korom S, et al. Extended donor lungs: eleven years experience in a consecutive series. Eur J Cardiothorac Surg 2005;27:762-7.
10. Straznicka M, Follette DM, Eisner MD, et al. Aggressive management of lung donors classified as unacceptable: excellent recipient survival one year after transplantation. J Thorac Cardiovasc Surg 2002;124:250-8.
11. Wilkes DS, Egan TM, Reynolds HY. Lung transplantation: opportunities for research and clinical advancement. Am J Respir Crit Care Med 2005;172:944-55.
12. Christie JD, Kotloff RM, Ahya VN, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 2005;171:1312-6.
13. de Perrot M, Liu M, Waddell TK, et al. Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med 2003;167:490-511.
14. Baldwin MR, Peterson ER, Easthausen I, et al. Donor age and early graft failure after lung transplantation: a cohort study. Am J Transplant 2013;13:2685-95.
15. Bittle GJ, Sanchez PG, Kon ZN, et al. The use of lung donors older than 55 years: a review of the United Network of Organ Sharing database. J Heart Lung Transplant 2013;32:760-8.
16. Fischer S, Gohrbandt B, Struckmeier P, et al. Lung transplantation with lungs from donors fifty years of age and older. J Thorac Cardiovasc Surg 2005;129:919-25.
17. Fessart D, Dromer C, Thumerel M, et al. Influence of gender donor-recipient combinations on survival after human lung transplantation. Transplant Proc 2011;43:3899-902.
18. Roberts DH, Wain JC, Chang Y, et al. Donor-recipient gender mismatch in lung transplantation: impact on obliterative bronchiolitis and survival. J Heart Lung Transplant 2004;23:1252-9.
19. International Society of Heart and Lung Transplantation Registry, Sato M, Gutierrez C, et al. The effect of gender combinations on outcome in human lung transplantation: the International Society of Heart and Lung Transplantation Registry experience. J Heart Lung Transplant 2006;25:634-7.
20. Thabut G, Mal H, Cerrina J, et al. Influence of donor characteristics on outcome after lung transplantation: a multicenter study. J Heart Lung Transplant 2005;24:1347-53.
21. Allen JG, Weiss ES, Merlo CA, et al. Impact of donor-recipient race matching on survival after lung transplantation: analysis of over 11,000 patients. J Heart Lung Transplant 2009;28:1063-71.
22. Bonser RS, Taylor R, Collett D, et al. Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. Lancet 2012;380:747-55.
23. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
24. Taghavi S, Jayarajan S, Komaroff E, et al. Double-lung transplantation can be safely performed using donors with heavy smoking history. Ann Thorac Surg 2013;95:1912-7; discussion 1917-8.
25. Berman M, Goldsmith K, Jenkins D, et al. Comparison of outcomes from smoking and nonsmoking donors: thirteen-year experience. Ann Thorac Surg 2010;90:1786-92.
26. Oto T, Griffiths AP, Levvey B, et al. A donor history of smoking affects early but not late outcome in lung transplantation. Transplantation 2004;78:599-606.
27. Weill D, Dey GC, Hicks RA, et al. A positive donor gram stain does not predict outcome following lung transplantation. J Heart Lung Transplant 2002;21:555-8.

28. Mattner F, Kola A, Fischer S, et al. Impact of bacterial and fungal donor organ contamination in lung, heart-lung, heart and liver transplantation. Infection 2008;36:207-12.
29. Campos S, Caramori M, Teixeira R, et al. Bacterial and fungal pneumonias after lung transplantation. Transplant Proc 2008;40:822-4.
30. Bonde PN, Patel ND, Borja MC, et al. Impact of donor lung organisms on post-lung transplant pneumonia. J Heart Lung Transplant 2006;25:99-105.
31. Bolton JS, Padia SA, Borja MC, et al. The predictive value and inter-observer variability of donor chest radiograph interpretation in lung transplantation. Eur J Cardiothorac Surg 2003;23:484-7.
32. McCowin MJ, Hall TS, Babcock WD, et al. Changes in radiographic abnormalities in organ donors: associations with lung transplantation. J Heart Lung Transplant 2005;24:323-30.
33. Barnard JB, Davies O, Curry P, et al. Size matching in lung transplantation: an evidence-based review. J Heart Lung Transplant 2013;32:849-60.
34. Eberlein M, Reed RM, Bolukbas S, et al. Lung size mismatch and survival after single and bilateral lung transplantation. Ann Thorac Surg 2013;96:457-63.
35. Hennessy SA, Hranjec T, Emaminia A, et al. Geographic distance between donor and recipient does not influence outcomes after lung transplantation. Ann Thorac Surg 2011;92:1847-53.
36. Fiser SM, Kron IL, Long SM, et al. Influence of graft ischemic time on outcomes following lung transplantation. J Heart Lung Transplant 2001;20:1291-6.
37. Gammie JS, Stukus DR, Pham SM, et al. Effect of ischemic time on survival in clinical lung transplantation. Ann Thorac Surg 1999;68:2015-9; discussion 2019-20.
38. Kshettry VR, Kroshus TJ, Burdine J, et al. Does donor organ ischemia over four hours affect long-term survival after lung transplantation? J Heart Lung Transplant 1996;15:169-74.
39. Winton TL, Miller JD, deHoyos A, et al. Graft function, airway healing, rejection, and survival in pulmonary transplantation are not affected by graft ischemia in excess of 5 hours. Transplant Proc 1993;25:1649-50.
40. Glanville AR, Marshman D, Keogh A, et al. Outcome in paired recipients of single lung transplants from the same donor. J Heart Lung Transplant 1995;14:878-82.
41. Meyer DM, Bennett LE, Novick RJ, et al. Effect of donor age and ischemic time on intermediate survival and morbidity after lung transplantation. Chest 2000;118:1255-62.
42. Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. Surgery 2011;150:692-702.
43. De Oliveira NC, Osaki S, Maloney JD, et al. Lung transplantation with donation after cardiac death donors: long-term follow-up in a single center. J Thorac Cardiovasc Surg 2010;139:1306-15.
44. De Vleeschauwer S, Van Raemdonck D, Vanaudenaerde B, et al. Early outcome after lung transplantation from non-heart-beating donors is comparable to heart-beating donors. J Heart Lung Transplant 2009;28:380-7.
45. Puri V, Scavuzzo M, Guthrie T, et al. Lung transplantation and donation after cardiac death: a single center experience. Ann Thorac Surg 2009;88:1609-14; discussion 1614-5.
46. Gomez-de-Antonio D, Campo-Cañaveral JL, Crowley S, et al. Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. J Heart Lung Transplant 2012;31:349-53.
47. Snell GI, Levvey BJ, Oto T, et al. Early lung transplantation success utilizing controlled donation after cardiac death donors. Am J Transplant 2008;8:1282-9.
48. Arnaoutakis GJ, Sodha NR, Tedford RJ, et al. Centers for Disease Control 'High-Risk' Donors and Thoracic Organ Transplantation: Expanding the Donor Pool. J Heart Lung Transplant 2013;32:S123.
49. Follette DM, Rudich SM, Babcock WD. et al. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. J Heart Lung Transplant 1998;17:423-9.
50. Zafar F, Khan MS, Heinle JS, et al. Does donor arterial partial pressure of oxygen affect outcomes after lung transplantation? A review of more than 12,000 lung transplants. J Thorac Cardiovasc Surg 2012;143:919-25.
51. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364:1431-40.
52. Steen S, Sjöberg T, Pierre L, et al. Transplantation of lungs from a non-heart-beating donor. Lancet 2001;357:825-9.
53. Ingemansson R, Eyjolfsson A, Mared L, et al. Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. Ann Thorac Surg 2009;87:255-60.
54. Pêgo-Fernandes PM, de Medeiros IL, Mariani AW, et al. Ex vivo lung perfusion: early report of Brazilian experience. Transplant Proc 2010;42:440-3.
55. Wallinder A, Ricksten SE, Hansson C, et al. Transplantation of initially rejected donor lungs after ex vivo lung perfusion. J Thorac Cardiovasc Surg

2012;144:1222-8.
56. Zych B, Popov AF, Stavri G, et al. Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. J Heart Lung Transplant 2012;31:274-81.
57. Aigner C, Slama A, Hötzenecker K, et al. Clinical ex vivo lung perfusion--pushing the limits. Am J Transplant 2012;12:1839-47.
58. Whiting D, Banerji A, Ross D, et al. Liberalization of donor criteria in lung transplantation. Am Surg 2003;69:909-12.
59. Moreno P, Alvarez A, Santos F, et al. Extended recipients but not extended donors are associated with poor outcomes following lung transplantation. Eur J Cardiothorac Surg 2014;45:1040-7.

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Review Article

Immunosuppression in lung transplantation

Jenna L. Scheffert[1], Kashif Raza[2]

[1]NewYork-Presbyterian Hospital/Columbia University Medical Center, Department of Pharmacy, USA; [2]Lung Transplant Program, Department of Pulmonary, Allergy and Critical Care Medicine, Columbia University Medical Center, USA

Correspondence to: Kashif Raza. 622 West 168th Street, PH 14-104, New York, NY 10032, USA. Email: kr2500@cumc.columbia.edu.

Abstract: Lung transplantation can be a life-saving procedure for those with end-stage lung diseases. Unfortunately, long term graft and patient survival are limited by both acute and chronic allograft rejection, with a median survival of just over 6 years. Immunosuppressive regimens are employed to reduce the rate of rejection, and while protocols vary from center to center, conventional maintenance therapy consists of triple drug therapy with a calcineurin inhibitor (cyclosporine or tacrolimus), antiproliferative agents [azathioprine (AZA), mycophenolate, sirolimus (srl), everolimus (evl)], and corticosteroids (CS). Roughly 50% of lung transplant centers also utilize induction therapy, with polyclonal antibody preparations [equine or rabbit anti-thymocyte globulin (ATG)], interleukin 2 receptor antagonists (IL2RAs) (daclizumab or basiliximab), or alemtuzumab. This review summarizes these agents and the data surrounding their use in lung transplantation, as well as additional common and novel therapies in lung transplantation. Despite the progression of the management of lung transplant recipients, they continue to be at high risk of treatment-related complications, and poor graft and patient survival. Randomized clinical trials are needed to allow for the development of better agents, regimens and techniques to address above mentioned issues and reduce morbidity and mortality among lung transplant recipients.

Keywords: Lung transplantation; immunosuppression; review

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Lung transplantation can be a life-saving procedure for those with end-stage lung diseases. Unfortunately, long term graft and patient survival are limited by both acute and chronic allograft rejection, with a median survival of just over 6 years (1). Immunosuppressive regimens are employed to reduce the rate of rejection, and while protocols vary from center to center, conventional maintenance therapy consists of triple drug therapy with a calcineurin inhibitor (cyclosporine or tacrolimus), antiproliferative agent [azathioprine (AZA), mycophenolate, sirolimus (srl), everolimus (evl)], and corticosteroids (CS). Roughly 50% of lung transplant centers also utilize induction therapy, with polyclonal antibody preparations [equine or rabbit anti-thymocyte globulin (ATG)], interleukin 2 receptor antagonists (IL2RAs) (daclizumab or basiliximab), or alemtuzumab (2). While these agents are used to prevent acute and chronic rejection, they are not without adverse effects, including drug-specific toxicities, as well as opportunistic infections and malignancy. This review will summarize these agents and the data surrounding their use in lung transplantation, as well as additional common and novel therapies in lung transplantation.

Induction immunosuppression

Induction therapy is intensive immunosuppressant therapy given perioperatively to reduce the risk of acute rejection and also serves to delay initiation of maintenance immunosuppression, most notably the nephrotoxic calcineurin inhibitors. These agents primarily target T lymphocytes, which are considered the effector cells in cell-mediated rejection.

According to the most recent registry report of the International Society for Heart and Lung Transplantation (ISHLT), of the centers that utilize induction, majority use an IL2RA (2). Both daclizumab and basilixmab are non-

Table 1 Induction immunosuppression

Citation	Immunosuppressant	N	Methods	Outcomes
Palmer *et al.* 1999 (7)	ATG *vs.* no induction	44	Prospective RCT	≥ A2 AR: 23% *vs.* 55%, P=0.03 BOS: 20% *vs.* 38% Survival, 1-yr: 68% *vs.* 73% Survival, 2-yr: 64% *vs.* 68% No difference in infection or malignancy
Garrity *et al.* 2001 (8)	Daclizumab *vs.* no induction	61	Retrospective	≥ A2 AR: 18% *vs.* 48%, P<0.04 No difference in infection or PTLD
Borro *et al.* 2005 (9)	Basiliximab *vs.* no induction	15	Retrospective	AR: 13% *vs.* 38.5%, P=0.19 BOS: 20% *vs.*38.5%, P=0.4 Survival, 2-yr: 80% *vs.* 54%, P=0.14 No difference in infection or malignancy
Hachem *et al.* 2005 (10)	Basiliximab *vs.* ATG	157	Retrospective	Cumulative A AR Score higher at 3-, 6-, 12-month with basiliximab, P=0.003, 0.004, 0.033 respectively BOS stage 1 at 2-yr: 36% *vs.* 26%
Burton *et al.* 2006 (11)	Daclizumab *vs.* ATG	335	Retrospective	Freedom from ≥ A2 AR, 3-month: 9% *vs.* 32% Freedom from ≥ A2 AR, 2-yr: 0% *vs.* 26% P<0.0001
Mullen *et al.* 2007 (12)	Daclizumab *vs.* ATG	50	RCT	No difference in AR or BOS at 1 year Survival: 96% *vs.* 88%
Ailawadi *et al.* 2008 (13)	Daclizumab *vs.* ATG	163	Retrospective	AR: 9% *vs.* 28%, P=0.002 BOS: 6.4% *vs.* 23%, P=0.02 Survival: 94% *vs.* 83%, P=0.05
Hartwig *et al.* 2008 (14)	ATG *vs.* no induction	44	Prospective RCT	AR: 62% *vs.* 68%, P=0.52 Early AR: 5% *vs.* 41%, P=0.01 Graft survival: 36% *vs.* 23%, P=0.048
Clinckart *et al.* 2009 (15)	Basiliximab *vs.* ATG	37	Retrospective	AR: 52.4% *vs.* 43.8%

RCT, randomized controlled trial; AR, acute rejection; BOS, bronchiolitis obliterans syndrome; PTLD, posttransplantlymphoprolifer ative disorder; ATG, anti-thymocyte globulin; yr, year.

depleting monoclonal antibodies that bind to the alpha subunit of the interleukin 2 (IL-2) receptor (CD25) present on activated T lymphocytes, thereby preventing T cell activation and proliferation (3,4). Daclizumab is a humanized (90% human, 10% murine) (3) monoclonal antibodythat was removed from the US market in 2009 (FDA), thus making basiliximab the only IL2RA available for use. Basiliximab is a chimeric (75% human, 25% murine) monoclonal antibody and is generally well tolerated, with adverse effects similar to that of placebo (4). ATG is the second most commonly used induction agent, used by roughly 20% of centers that utilize induction (2). ATG is a polyconal antibody preparation isolated from either rabbit (rATG, Thymoglobulin©) or horse (equine ATG, ATGAM©) sera which contain antibodies toward human thymocytes and cause significant T cell depletion (5,6). Adverse effects associated with these agents include fever, chills, rash, arthralgia, diarrhea, leukopenia, and thrombocytopenia. Pre-medication with acetaminophen, anti-histamines, and CS are usually required and help minimize these reactions. Serum sickness and anaphylaxis have also been reported, in addition to increased rates of infection and malignancy.

Data for the use of induction in lung transplantation are presented in *Table 1*. Overall it appears that induction with either ATG or an IL2RA reduces or delays the incidence of acute rejection, bronchiolitis obliterans syndrome (BOS), and may improve graft and patient survival compared to no induction (7-9,14). Studies comparing IL2RAs and ATG

show inconclusive results; one study indicated IL2RAs are associated with lower rates of acute rejection and BOS, as well as improved survival (13); three studies showed lower acute rejection and BOS and improved survival with ATG (10,11,15), while still another showed no difference (12). In 2008, Hachem and colleagues published a registry report that retrospectively analyzed 3,970 adult lung transplant recipients. Four year graft survival in those who received induction with an IL2RA, ATG, or no induction were 64%, 60%, and 57% (P=0.0067), respectively (16). Reasons for such variability in outcomes relate to the size and retrospective nature of these studies, potential differences in patient population and management, duration of followup, and variability in maintenance immunosuppression regimens. More recently, alemtuzumab, a humanized monoclonal antibody targeting CD52, has been used as an induction agent. The CD52 antigen is found on T and B lymphocytes, as well as natural killer cells, monocytes and macrophages (17). Upon binding, alemtuzumab induces cellular lysis and causes significant and prolonged depletion, with B cell recovery occurring within 3-6 months and T cell recovery >12 months (18,19). This profound and prolonged lymphocyte depletion associated with alemtuzumab may allow for the possibility of reduced maintenance immunosuppression. Loenhout and colleagues published their findings using alemtuzumab induction in 20 lung transplant recipients with reduced maintenance immunosuppression in 2010. Compared to 20 historical controls who received standard maintenance immunsuppression, there were no statistical differences between 6- or 12-month survival (95% *vs.* 90%, 76% *vs.* 95%), episodes of acute rejection (2/16 *vs.* 5/20), or bacterial, viral or fungal infections (20). Subsequently, Shyu and colleagues published 5 year outcomes using alemtuzumab induction with reduced-intensity maintenance immunosuppression. Their retrospective analysis grouped patients according to induction type: alemtuzumab (n=127), ATG (n=43), daclizumab (n=73), or none (n=93). Graft survival differed by group: 59%, 44%, 41%, 47%, respectively; as did freedom from acute rejection: 30%, 20%, 19%, 18%, respectively; freedom from lymphocytic bronchiolitis: 82%, 54%, 55%, 70% respectively; and freedom from BOS: 54%, 27%, 43%, 46% respectively (21). While alemtuzumab induction with reduced maintenance immunosuppression thus far demonstrates similar if not improved overall outcomes compared to other induction regimens, the optimal induction and maintenance regimen still needs to be elucidated by large, randomized controlled trials. Though 50% of centers currently utilize induction, enhanced immunosuppression must be weighed against adverse effects, including infection and malignancy. Large, randomized controlled trials measuring the difference in acute rejection, BOS, graft and patient survival, infection and malignancy comparing no induction, IL2RAs, ATG, and alemtuzumab are needed to better understand the effect of the agents and to identify the optimal regimen for lung transplant recipients.

Maintenance immunosuppression

Maintenance immunosuppression is lifelong immunosuppressive therapy that is given to prevent both acute and chronic rejection. The goal is to not only to prevent and minimize immune-mediated injury to the allograft but also to minimize adverse effects associated with the medications used. Conventional maintenance immunosuppressive regimens consist of triple drug therapy with a calcineurin inhibitor, antiproliferative agent, and CS. Historically cyclosporine and AZA were used along with prednisone, but over time additional agents have emerged on the market, including tacrolimus, mycophenolate, and the mammalian target of rapamycin (mTOR) inhibitors, srl and evl. Despite the addition of these agents to the armamentarium of immunosuppression for lung transplant recipients, acute rejection and BOS remain obstacles to long-term survival. Additionally, minimization and management of adverse effects continuesto be challenging. Selection of regimens is largely protocolized and based on studies from other types of organ transplantation as well as currently available literature in lung transplant, and center-specific outcomes and provider experience.

Calcineurin inhibitors

Cyclosporine was the first calcineurin inhibitor available for use, first approved by the FDA in 1983. It is a lipophilic compound that binds to intracellular cyclophilin in T lymphocytes, forming a complex that prevents transcription of interleukin 2, thereby decreasing activation and proliferation of T lymphocytes (22). Oral absorption of cyclosporine (Sandimmune©) is poor and variable (10-89%). A modified cyclosporine formulation was subsequently developed and approved by the FDA in 1997 (Neoral©) with enhanced bioavailability, with approximately 50-150% increases in area under the curve (AUC) and Cmax (23,24). Sandimmune and Neoral are not interchangeable but both are available in capsules, oral solution, and intravenous

formulations. Therapeutic drug monitoring of cyclosporine consists of measuring trough (C0) values, AUC calculations, or 2-hour post-dose (C2) levels. In renal transplantation, AUC measurements have demonstrated superiority over troughs (25), however this requires multiple samples to estimate AUC, which is time consuming, cumbersome and impractical. A limited sampling strategy (LSS) may be employed as an alternative, measuring 2 post-dose levels (26), but this method still requires multiple samples and a calculation to estimate AUC. Therefore most centers utilize either C0 or C2 levels. Studies in lung transplant recipients indicate that C2 is a better correlate with AUC than C0 (27) and may reduce short-term nephrotoxicity associated with cyclosporine compared with C0, without compromising lung function (28). Target ranges vary according to center-specific protocols and practices, and take into account patient characteristics, such as time post-transplant and rejection and infection history. Generally, target trough levels range from 100-450 ng/mL, or C2 levels 800-1,400 ng/mL. Major adverse effects of cyclosporine include nephrotoxicity (acute and chronic), hypertension, hypercholesterolemia, electrolyte abnormalities (hyperkalemia, hypomagnesemia), neurotoxicity (posterior reversible encephalopathic syndrome, seizures, headache, tremor), diabetes, hirsutism, and gingival hyperplasia. A second calcineurin inhibitor, tacrolimus(previously known as FK506) (Prograf©) became available for use in 1997. It is 10-100 times more potent than cyclosporine. Tacrolimus binds to intracellular FKBP12, forming a complex that prevents transcription of cytokines, including interleukin 2, and ultimately prevents T lymphocyte activation and proliferation (29). Like cyclosporine, tacrolimus has poor and variable absorption, 17-23% (29). Tacrolimus is available in oral capsules and as an intravenous formulation. There is no commercially available oral suspension however formulas for pharmaceutical compounding are available. Sublingual administration of tacrolimus capsules at half of the oral dose is an option for those who are unable to tolerate oral therapy and wish to avoid intravenous tacrolimus due to significant toxicity (30). A once-daily extended-release formulation of tacrolimus, marketed under the trade name Astragraf XL® was approved by the FDA in 2013. No studies have yet been performed in lung transplant recipients; however they may be available in the future. Despite multiple studies indicating post-dose levels to more accurately predict AUC, most centers utilize trough concentrations for therapeutic drug monitoring (31,32). Target ranges vary according to center-specific protocols and practices, and take into account patient characteristics, such as time post-transplant and rejection and infection history. Generally, target trough concentrations range from 5-15 ng/mL. Tacrolimus displays similar adverse effects to cyclosporine, with perhaps less hypertension and hypercholesterolemia, but more neurotoxicity and diabetes (33-39). Thrombotic thrombocytopenia purpura and hemolytic uremic syndrome have been reported with both cyclosporine and tacrolimus (40). Both cyclosporine and tacrolimus undergo metabolism via the hepatic cytochrome (CYP) P450 3A4 and 3A5 enzymes and p-glycoprotein efflux pumps present on intestinal mucosa,leading to significant drug interactions with CYP inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) and inhibitors (e.g., azoles, macrolides, calcium channel blockers). Additional drug interactions exist for cyclosporine, as it is not only a substrate of CYP 3A4 but also a moderate inhibitor (statins).

Selected data comparing cyclosporine and tacrolimus are shown in *Table 2*. Majority of the trials are small, prospective, randomized studies showing no statistical differences in acute rejection or survival between those treated with cyclosporine or tacrolimus, whether receiving no induction or ATG, AZA or mycophenolate. The most recent study published in 2012 by Treede *et al.* is the largest study to date and showed no difference between cyclosporine and tacrolimus in acute rejection or survival at 3-year, however there was a higher incidence of BOS stage 1 or greater with cyclosporine and it was also shown to be a risk factor for the development of BOS by univariate analysis (46). According to the most recent ISHLT Registry report, tacrolimus was the most frequently used calcineurin inhibitor, 83% at one year post-transplant, 77% at 5 years post-transplant (2).

Anti-proliferative agents

AZA was the first anti-proliferative agent available for use. AZA is converted to 6-mercaptopurine (6-MP) in vivo which then is converted into several compounds that get incorporated into the DNA of replicating cells and halt proliferation (47). AZA is associated with significant leukopenia, thrombocytopenia, anemia, hepatotoxicity (transaminitis and cholestasis), and rarely pancreatitis. Caution must be used when using AZA with xanthine oxidase (XO) inhibitors (e.g., allopurinol). XO is thought to be responsible for converting 6-MP to metabolites. The combination results in significant bone marrow suppression

Table 2 Maintenance immunosuppression

Citation	Immunosuppressant	N	Methods	Outcomes
Griffith *et al.* 1994 (41)	FK506 *vs.* CsA	74	Prospective, randomized	AR: 1.2 *vs.* 2 episodes per 100 patient days, P<0.05 Survival, 1-yr: no difference Bacterial infection: 0.6 *vs.* 1.5 episodes per 100 patient days, P= NS
Treede *et al.* 2001 (42)	Tac *vs.* CsA	50	Prospective, randomized	Freedom from AR, 1 yr: 50% *vs.* 33.3%, P= NS Treated episodes of AR/100 patient days: 0.225 *vs.* 0.426, P<0.05 Survival, 1 yr: 73.1% *vs.* 79.2%, P= NS No difference in infection
Zuckerman *et al.* 2003 (43)	Tac *vs.* CsA	74	Prospective, randomized	Freedom from AR, 1-yr: 46% *vs.* 35%, P=0.774 Treated episodes of AR/100 patient days: 0.22 *vs.* 0.32, P=0.097 Survival, 1-yr: 71% *vs.* 82%, P=0.748 Infections: 0.55 *vs.* 0.7, P=0.059
Hachem *et al.* 2007 (44)	Tac *vs.* CsA	90	Prospective RCT	Composite (Cumulative ≥ A3 AR, ≥ B4 LB, BOS 0-p): 50% *vs.* 84.8%, P=0.002 AR or LB: 41% *vs.* 63%, P=0.036 Freedom from BOS 0-p: Tac > CsA, P=0.1
Neurohr *et al.* 2009 (45)	Tac + MMF	155	Retrospective	Freedom from AR, 1-yr: 74.6% Freedom from AR, 5-yr: 59.5% Freedom from BOS, 1-yr: 95.6% Freedom from BOS, 5-yr: 69.5% Survival, 1-yr: 86.4% Survival, 5- yr: 60.3%
Treede *et al.* 2012 (46)	Tac *vs.*CsA	249	Prospective, randomized	AR, 3-yr: 67.4% *vs.* 74.9%, P=0.118 BOS ≥ stage 1-, 3-yr: 11.6% *vs.* 21.3%, P=0.037 Survival, 1-yr: 84.6% *vs.* 88.6% (NS) Survival, 3-yr: 78.7% *vs.* 82.8% (NS) No difference in infection

FK506, tacrolimus; CsA, cyclosporine;AR, acute rejection; NS, not statistically significant; Tac, tacrolimus; RCT, randomized controlled trial; LB, lymphocytic bronchiolitis; BOS, bronchiolitis obliterans syndrome; MMF, mycophenolate mofetil; yr: year.

and a 75% dose reduction of AZA in combination with XO inhibitors is generally recommended. The typical starting dose is 2 mg/kg IV or orally daily.

Mycophenolate is the most frequently used antiproliferative agent used according to the most recent ISHLT Registry report (2). Mycophenolate mofetil and mycophenolate sodium are converted to the active metabolite, mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH), the enzyme responsible for T and B lymphocyte production. Inhibiting this enzyme results in decreased T and B lymphocyte proliferation. Because lymphocytes lack the ability to utilize salvage pathways for nucleotide synthesis and thus rely on the IMPDH pathway, mycophenolate is selective for T and B lymphocyte proliferation inhibition (47). Mycophenolate undergoes rapid absorption and conversion to MPA. MPA is metabolized hepatically into mycophenolic acid glucuronide (MPAG). MPAG is excreted via bile into the intestines, where it is converted back to the active metabolite, MPA, resulting in a second peak concentration in the plasma. Doses range from 1-1.5 g IV or oral twice daily. Therapeutic drug monitoring is available for mycophenolate, with AUC being the optimal parameter for measuring treatment response. Trough values have

shown poor predictive response (48-50). LSS calculations for estimation of AUC in lung transplant patients are also availablehowever therapeutic drug monitoring has not been firmly established (51). Principle adverse effects of mycophenolate are leukopenia, thrombocytopenia, and gastrointestinal disturbances (diarrhea, abdominal pain, nausea, vomiting). Initial use of mycophenolate involved rescue therapy following development of BOS, with stabilization of pulmonary function testing after switching from AZA (52). In a prospective, randomized trial of 81 lung transplant recipients comparing azathiopine to mycophenolate in combination with cyclosporine and CS, there were no differences in biopsy-proven or clinical rejection, survival, infection, or adverse drug events at 6-month (53). A subsequent prospective, randomized multicenter study comprising 315 lung transplant recipients also showed no difference between AZA and mycophenolate when used in combination with cyclosporine and CS in the outcomes of acute rejection, BOS, and survival at 3-year, however a greater percentage of patients discontinued AZA than mycophenolate (59.6% *vs.* 46.5%) (54).

Srl and evl are two newer antiproliferatives in the mTOR inhibitor class. Both bind to intracellular immunophilin FK506 binding protein like tacrolimus, however unlike tacrolimus the complexes they form do not inhibit calcineurin but instead bind to mTOR, which is a signaling pathway needed to promote progression of the cell cycle from G1 to S phase. The end effect of mTOR inhibitors is a decrease in T lymphocyte activation and proliferation (47). Srl is available as oral tablets and an oral solution. Doses range from 0.5-6 mg daily, with target trough values ranging 5-15 ng/mL. Evl is available as oral tablets. Doses range from 0.25-3 mg twice daily, with target trough values ranging 5-15 ng/mL. Notable adverse effects include decreased wound healing, leukopenia, thrombocytopenia, hypertriglyceridemia, proteinuria, and pneumonitis. Both are metabolized by CYP 3A4 and therefore have similar drug interactions as tacrolimus. The role of mTOR inhibitors in lung transplant is still being identified. They may be used in conjunction with or substituted for either calcineurin inhibitors or other antiproliferative agents. The most common reasons for use include kidney dysfunction due to calcineurin inhibitors, onset of BOS, and malignancy (55-57). For those who exhibit kidney dysfunction, adding an mTOR inhibitor and reducing the calcineurin inhibitor dose has been shown to improve kidney function (55,58,59).Additionally, due to their antiproliferative and anti-fibroblast effects (60), mTOR inhibitors have been used in lung transplant recipients with BOS to help slow progression. Indeed small, retrospective studies have shown stabilization or improvement in pulmonary function testing in lung transplant recipients with BOS (55,56,61,62). Two studies used srl immediately post-transplant and reported significant wound dehiscence and airway complications, leading to death in some patients (63,64), so mTOR inhibitors should not be used until the anastomosis and airways have healed. In 2006, Snell and colleagues performed a prospective randomized controlled trial comparing AZA and 3th month conversion to evl in 213 lung transplant recipients also maintained on cyclosporine and CS. The composite endpoint of efficacy failure (>15% FEV_1 decline from baseline, graft loss, death or loss to follow up) occurred in 33.9% *vs.* 21.8% of patients at 12-month (P=0.046), however there was no difference in this composite endpoint at 24-month. The authors concluded that evl did demonstrate a slowing in loss of pulmonary function over time (65). Most recently, Sacher and colleagues published data on 24 lung transplant recipients who were converted to srl prophylactically *vs.* AZA/MMF, one year post-transplant. Of the 19 patients who remained on long-term srl, a trend toward a reduction in the incidence of BOS and improved survival was reported (66). Larger, randomized controlled trials are needed to more fully elucidate the effect of mTOR inhibitors in the prevention of BOS.

Corticosteroids (CS)

CS have been used in solid organ transplant since the very beginning and have not only remained a corner stone of both induction and maintenance immunosuppression but they are also used to treat acute cellular rejection (ACR) as well. The most commonly used CS in solid organ transplant are methylprednisolone and prednisone. CS are known to have antiinflammatory properties and exert their effects in a variety of ways, including inhibiting the NFkB pathway, preventing T cell proliferation, decreasing macrophage activation, inhibitingcytokine production and altering lymphocyte migration (67). According to the most recent ISHLT registry report, CS continue to be used by almost all transplant centers, at one and five years post-transplant. Initial doses range from 500-1,000 mg given intraoperatively, and are gradually tapered over weeks to months to 5-10 mg per day for maintenance. Short and long term use of CS is associated with significantside effects, including hypertension, weight gain, hyperlipidemia, hyperglycemia and diabetes mellitus, osteoporosis and increased risk of fractures, increased risk of cataracts, poor

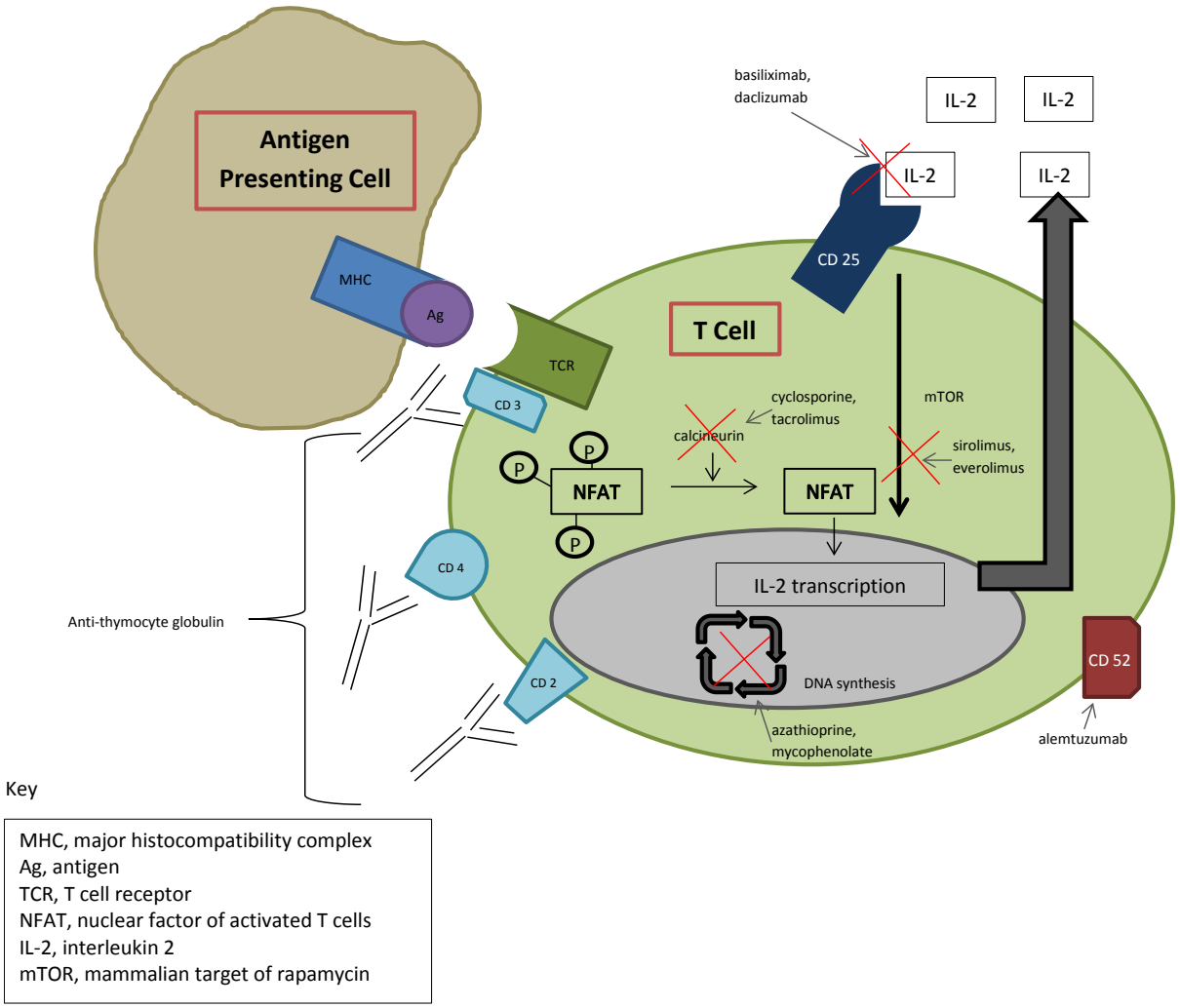

Figure 1 Mechanisms of action of immunosuppressive agents.

wound healing, psychiatric disturbances and infectious complications.Data on steroid-free regimens in lung transplantation is lacking and at best shows limited success (68,69). Complete steroid-withdrawal should be avoided at the present time, owing to a significant risk of allograft dysfunction; however, doses should be lowered as quickly and as safely as possible, and maintainthe lowest possible doses with the goal of stable and optimal lung function while avoiding and minimizing drug-related adverse effects (*Figure 1*).

Antihumoral therapy

Generally immunosuppression is employed to suppress cell mediated immunity by targeting T cell function and proliferation as rejection is usually a cell mediated phenomenon. However the role of humoral or antibody-mediated rejection (AMR) in solid organ transplant recipients has become more evident over the years. Antibody mediated rejection has been identified and characterized in other organs but remains poorly defined in lung transplant recipients. No agreed upon pathologic criteria exists to date in lung transplantation (70,71). Mechanisms by which anti bodies, which usually are donor specific antibodies (DSA), produce injury are not yet well described. Injury may be complement mediated or complement independent (72). No universally agreed upon management strategy exists for these antibodies. Use of intra venous immunoglobulin (IVIG), one of most commonly used treatments with a relatively low side effect

profile, with or without plasmapheresis, peritransplant and after development of DSA post-transplant resulted in improvement in certain parameters such as acute rejection and BOS at a single institution (73). In a study reported by Hachem and colleagues, use of IVIG combined with rituximab, a monoclonal anti CD20 antibody, *vs.* IVIG to clear newly acquired DSA showed improved survival and freedom from BOS in patients who cleared DSA after treatment. However there was no improvement in clearance of DSA with addition of rituximab to IVIG (74). Plasmapheresis is mainly used for antibody removal from circulation in suspected cases of humoral rejection which do not respond to steroids, leading to clinical improvement (75). Bortezomib, an inhibitor of 26S proteasome that leads to plasma cell apoptosis, has been used successfully in case reports to treat possible acute humoral rejection in lung transplant recipients (76,77). Hyperacute rejection due to pre formed antibodies against donor HLA antigens has become uncommon due to ongoing cross match screening. Treatment with IVIG, plasmaphresis, rituximab, antithymocyte globulin and eculizumab has been described in various case reports with variable degree of success (78-80).

Novel approaches

Aerosolized calcineurin inhibitors

A number of reports have been published regarding the use of aerosolized cyclosporine. In 1996, Iacono and colleagues published a report of histologic improvement of obliterative bronchiolitis (OB) and stabilization of pulmonary function testing in 7 lung transplant recipients who received aerosolized cyclosporine as rescue therapy (81). Shortly thereafter, the use of aerosolized cyclosporine to treat refractory acute rejection in 9 lung transplant recipients was associated with histologic improvement in 8 of 9 subjects, improvement in pulmonary function testing, a reduction in cycles of pulse dose CS and ATG, reduction in oral prednisone dose, and reduction in episodes of pneumonia was also observed, compared to 22 historical controls (82). Both reports showed no additional renal or hepatic toxicity with the use of aerosolized cyclosporine. A larger case-control study was subsequently undertaken and demonstrated a survival advantage in lung transplant recipients with biopsy-documented OB compared to conventional immunosuppression (83). While the most well-studied randomized placebo-controlled trial of aerosolized cyclosporine did not show a reduction in the primary endpoint of rate of ACR, it also demonstrated a survival advantage compared with conventional immunosuppression, and showed an improvement in chronic rejection-free survival (84). Despite these results, an FDA-approved formulation of aerosolized cyclosporine is still currently unavailable. Animal studies aiming to characterize aerosolized tacrolimus pharmacokinetics and safety have been published (85-87). The first case report of using tacrolimus via inhalation in a human lung transplant recipient with BOS was recently published demonstrating improved functional capacity and oxygenation after one week of therapy (88). More data are needed to determine the optimal use of aerosolized calcineurin inhibitors but this therapeutic approach seems promising.

Azithromycin

Azithromycin is a macrolide antibiotic with anti-inflammatory and immunomodulatory effects (89). These effects, in conjunction with the beneficial effects of maintenance azithromycin seen in cystic fibrosis patients led to pilot studies of azithromycin in lung transplant recipients with BOS (90-93). In 5 of 6 patients, thrice-weekly azithromycin for 13 weeks demonstrated an average 17% improvement in FEV_1 (92) and an average 18% improvement in FEV_1 after 12 weeks of therapy in 8 others (93). A retrospective analysis of 20 lung transplant recipients also demonstrated an improvement in FEV_1 after 12 weeks of azithromycin therapy (average 110 mL from baseline) (94). However, not all patients respond to azithromycin therapy (95-97). Evidence suggests airway neutrophilia and elevated interleukin-8 bronchoalveolar (BAL) concentration may be predictors of response (95,97,98). Furthermore, studies have indicated that early initiation of azithromycin, e.g., BOS 0-p, may have more of an impact on preventing disease progression and may improve survival (97,99,100). In a randomized, placebo-controlled trial of 83 lung transplant recipients, there was a significant reduction in the incidence of BOS at 2-year in those who received azithromycin prophylactically compared to those who did not (12.5% *vs.* 44.2%, P=0.0017) (101). There was also a significant difference in BOS-free survival (HR 0.27, P=0.020), although overall survival was similar between groups. Collectively these data suggest early initiation of azithromycin in lung transplant recipients may prevent the incidence of BOS and prolong BOS-free survival, and may improve or stabilize pulmonary function after the onset of BOS, particularly in those with neutrophil- and IL-8-predominant BAL.

Extracorporeal photopheresis (ECP)

ECP was developed initially for treatment of cutaneous T cell lymphomabut has been utilized in variety of disease states including solid organ transplantation. The process involves leukopheresis followed by incubation of the isolated cells with 8-methoxypsoralen (8-MOP) and subsequent activation of 8-MOP with ultraviolet A radiation. These cells are then reinfused into the patient. 8-MOP activation causes DNA cross linkage and apoptosis. Reinfusion of these apoptotic cells generate T regulatory cells (T regs) and increased production of IL-10 and transforming growth factor beta. Exact mechanisms by which these immunomodulatory effects are produced are not well understood. At present, clinical studies assessing efficacy of ECP in lung transplant recipients are limited to retrospective single center studies done in patients showing declining lung function. No trials to assess the prophylactic effect of ECP on development of BOS by starting ECP immediately post-transplant have been done to date. In a study by Morrell and colleagues, 60 lung transplant patients received ECP in addition to conventional immunosuppression for treatment of progressive BOS. Fifteen patients (25%) showed an improvement in FEV_1 and rest showed a reduction in rate of decline in FEV_1 which persisted at 12 months after initiation of ECP (102). Another study done by Jaksch and colleagues, 51 lung transplant recipients who developed BOS and did not respond to augmentation of immunosuppression and azithromycin, received ECP.Thirty-one patients (61%) showed improvement or stabilization of lung function while 20 patients (39%) had continued decline in lung function and did not respond to ECP. Survival rate after start of BOS at 1, 3 and 5 years was significantly better in treatment responsive group (103).These studies did not identify any significant characteristics among lung transplant recipients that could predict the response to ECP. Recently a retrospective single center study done by Greer and colleagues assessed clinical efficacy of ECP treatment in lung transplant recipients with azithromycin-refractory chronic lung allograft dysfunction (CLAD) and attempted to associate clinical response to several CLAD phenotypes. Sixty-five lung transplant recipients were diagnosed and graded for graft dysfunction in accordance with ISHLT BOS criteria and were started on ECP treatment while showing deterioration or no improvement despite taking azithromycin which was started after reversible causes of graft dysfunction were excluded. Thirty-five patients (54%) showed improvement or stabilization of FEV_1 while 30 patients showed >10% decline in FEV_1. Three CLAD phenotypes, restrictive allograft syndrome, defined by TLC ≤90% of baseline, non neutrophilic CLAD, patients demonstrating BAL neutrophilia <15% and rapid decliners, patients suffering a >100 mL/month decline in FEV_1 before ECP initiation showed that they were less likely to benefit from ECP treatment. Significant survival benefit was noted in the ECP responsive group when compared to the ECP refractory group (104). Randomized clinical trials are needed to better evaluate the benefit and possibility of early use of ECP after onset of CLAD in lung transplant recipients.

Statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme Areductase inhibitors, have been shown to have properties which may have a potential beneficial impact on lung allograft function post-transplant. They have been shown to reduce the gamma interferon induced expression of major histocompatibility molecules on cells, increase the number of $CD4^+CD25^+$ T regs, inhibit growth factor expression in lung fibroblasts and inhibit the development of obliterative airway disease in animal models (105-108).

These abovementioned immunomodulatory and anti-fibroproliferative properties have potential benefit for lung transplant recipients. However, clinical evidence in lung transplant recipients is limited to retrospective single center studies only. Johnson and colleagues showed improved 6-year survival in statin group compared to controls, 91% *vs.* 54%, as well as reduced rates of acute rejection and BOS (109). Li and colleagues showed improved survival and maintenance of lung function associated with post-transplant use of simvastatin in a single center cohort analysis of 502 lung transplant recipients (110). Prospective randomized trials are needed to confirm these findings, compare different statins and determine the optimal dose.

Pirfenidone

Pirfenidone is an anti-fibrotic agent used to treat pulmonary fibrosis. It inhibits growth-factor dependent proliferation of fibroblasts, T cell proliferation and activation, and may inhibit dendritic cell activation and function (111-115), and may be a potential therapeutic strategy for the treatment of CLAD. Thus far two case reports of pirfenidone use in human lung transplant have been published (116,117). The first reported a mild increase in FEV_1 following progressive

Table 3 Summary of stages and types of therapy

Induction immunosuppressants (Goal: prevent acute cellular and antibody-mediated rejection; delay initiation of nephrotoxic immunosuppressants)
Interleukin 2 receptor antagonists (non-depleting monoclonal antibody)
Daclizumab (Zenapax©)
Basiliximab (Simulect©)
Anti-thymocyte globulin (cell depleting polyclonal antibody preparation)
Equine (ATGAM©)
Rabbit (Thymoglobulin©)
Anti-CD 52 monoclonal antibody (cell-depleting)
Alemtuzumab (Campath©)
Maintenance immunosuppressants (Goal: prevent acute cellular antibody-mediated rejection; prevent chronic lung allograft dysfunction)
Calcineurin inhibitors
Cyclosporine (Sandimmune©, Neoral©)
Tacrolimus (Prograf©)
Anti-proliferative agents
Azathioprine (Imuran©)
Mycophenolatemofetil (CellCept©)
mTOR inhibitors
Sirolimus (Rapamune©)
Everolimus (Zortress©)
Corticosteroids
Methylprednisolone (Solu-Medrol©, Medrol©)
Prednisone (Deltasone©)
Acute cellular rejection, treatment
Methylprednisolone (Solu-Medrol©, Medrol©)
Anti-thymocyte globulin (Thymoglobulin©)
Alemtuzumab (Campath©)
Antibody-mediated rejection, treatment
Plasmapheresis
IVIG
Rituximab (Rituxan©)
Bortezomib (Velcade©)
Chronic lung allograft dysfunction, treatment
Azithromycin (Zithromax©)
Extracorporeal photopheresis
Statins
Pirfenidone

IVIG, intra venous immunoglobulin.

decline with no evidence of infection or rejection and failure to respond to azithromycin, montelukast and fundoplication (116). The second reported a slower rate of decline in forced vital capacity, FEV_1, and a mild increase in total lung capacity in a lung transplant recipient with restrictive allograft syndrome (117). Given these findings, further study of pirfenidone in human lung transplantation is warranted.

Treatment

ACR, AMR and CLAD are discussed in-depth elsewhere. Specific treatment protocols vary from center to center, but options are limited to high-dose or "pulse" CS (e.g., methylprednisolone 10-15 mg/kg IV daily × 3-5 days), particularly for initial treatment or minimal-mild grade ACR; ATG (1.5 mg/kg IV daily × 3-5 days) or alemtuzumab (30 mg IV once) for moderate-severe grade ACR or steroid-resistant/steroid-refractory ACR. Therapies available for treatment of AMR include plasmaphereis (5-6 cycles), IVIG (1-2 g/kg over 3-6 days), rituximab (375 mg/m^2 IV weekly × 4 doses or 1,000 mg IV every 2 weeks × 2 doses), and/or bortezomib (1-1.3 mg/m^2 every 72 hours × 4 doses). Treatment options for CLAD are even more limited, and there is currently no agent available to date that reverses that process and restores lung function, other than re-transplant when available. Therapies targeting the processes of CLAD either prevent the onset of CLAD, or prevent and delay its progression. These include azithromycin, ECP, the statins, and pirfenidone. Augmentation of immunosuppression with ATG, alemtuzumab, addition or substitution of an mTOR inhibitor to the maintenance regimen, substitution of mycophenolate for AZA or of tacrolimus for cyclosporine, are additional strategies that have been employed with varying success (*Table 3*).

Summary

Our understanding of the underlying mechanisms and clinical presentation of acute allograft rejection and CLAD continue to evolve. Immunosuppressive regimens have significantly contributed to the improvement of the survival of lung transplant recipients. Despite the progress in the management of lung transplant recipients, they continue to be at high risk of treatment-related complications, poor allograft and patient survival. Randomized clinical trials are needed to allow the development of better agents, regimens and techniques to address above mentioned issues

and reduce morbidity and mortality among lung transplant recipients.

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References

1. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report--2013; focus theme: age. International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2013;32:965-78.
2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. International Society of Heart and Lung Transplantation. J Heart Lung Transplant 2012;31:1073-86.
3. Zenapax® [package insert]. Nutley, NJ: Roche Pharmaceuticals, 2005.
4. Simulect® [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation, 2005.
5. Thymoglobulin® [package insert]. Cambridge, MA: Genzyme, 2008.
6. ATGAM [package insert]. New York, NY: Pfizer Pharmacia and Upjohn Company, 2005.
7. Palmer SM, Miralles AP, Lawrence CM, et al. Rabbit antithymocyte globulin decreases acute rejection after lung transplantation. Chest 1999;116:127-33.
8. Garrity ER, Villanueva J, Bhorade SM, et al. Low rate of acute lung allograft rejection after the use of daclizumab, an interleukin 2 receptor antibody. Transplantation 2001;71:773-7.
9. Borro JM, De la Torre M, Miguelez C, et al. Comparative study of basiliximab treatment in lung transplantation. Transplant Proc 2005;37:3996-8.
10. Hachem RR, Chakinala MM, Yusen RD, et al. A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. J Heart Lung Transplant 2005;24:1320-26.
11. Burton CM, Andersen CB, Jensen AS, et al. The incidence of acute cellular rejection after lung transplantation: a comparative study of anti-thymocyte globulin and daclizumab. J Heart Lung Transplant 2006;25:638-47.
12. Mullen JC, Oreopoulos A, Lien DC, et al. A randomized, controlled trial of daclizumabvs anti-thymocyte globulin induction for lung transplantation. J Heart Lung Transplant 2007;26:504-10.
13. Ailawadi G, Smith PW, Oka T, et al. Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. J Thorac Cardiovasc Surg 2008;135:594-602.
14. Hartwig MG, Snyder LD, Appel JZ, et al. Rabbit anti-thymocyte globulin induction therapy does not prolong survival after lung transplantation. J Heart Lung Transplant 2008;27:547-53.
15. Clinckart F, Bulpa P, Jamart J, et al. Basiliximab as an alternative to antithymocyte globulin for early immunosuppression in lung transplantation. Transplant Proc 2009;41:607-9.
16. Hachem RR, Edwards LB, Yusen RD, et al. The impact of induction on survival after lung transplantation: an analysis of the international society for heart and lung transplantation registry. Clin Transplant 2008;22:603-8.
17. Campath® [package insert]. Cambridge, MA: Genzyme, 2009.
18. Heidt S, Hester J, Shankar S, et al. B cell repopulation after alemtuzumab induction-transient increase in transitional B cells and long-term dominance of naïve B cells. Am J Transplant 2012;12:1784-92.
19. Noris M, Casiraghi F, Todeschini M, et al. Regulatory T cells and T cell depletion: role of immunosuppressive drugs. J Am Soc Nephrol 2007;18:1007-18.
20. van Loenhout KC, Groves SC, Galazka M, et al. Early outcomes using alemtuzumab induction in lung transplantation. Interact Cardiovasc Thorac Surg 2010;10:190-4.
21. Shyu S, Dew MA, Pilewski JM, et al. Five-year outcomes with alemtuzumab induction after lung transplantation. J Heart Lung Transplant 2011;30:743-54.
22. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. Immunopharmacology 2000;47:119-25.
23. Neoral® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2013.
24. Trull A, Steel L, Sharples L, et al. Randomized, trough blood cyclosporine concentration-controlled trial to compare the pharmacodynamics of Sandimmune and Neoral in de novo lung transplant recipients. Ther Drug Monit 1999;21:17-26.
25. Grevel J, Welsh MS, Kahan BD. Cyclosporine monitoring in renal transplantation: area under the curve monitoring is superior to trough-level monitoring. Ther Drug Monit 1989;11:246-8.

26. Dumont RJ, Partovi N, Levy RD, et al. A limited sampling strategy for cyclosporine area under the curve monitoring in lung transplant recipients. J Heart Lung Transplant 2001;20:897-900.
27. Jaksch P, Kocher A, Neuhauser P, et al. Monitoring C2 level predicts exposure in maintenance lung transplant patients receiving the microemulsion formulation of cyclosporine (Neoral). J Heart Lung Transplant 2005;24:1076-80.
28. Morton JM, Aboyoun CL, Malouf MA, et al. Enhanced clinical utility of de novo cyclosporine C2 monitoring after lung transplantation. J Heart Lung Transplant 2004;23:1035-9.
29. Prograf® [package insert]. Northbrook, IL: AstellasPharma US, Inc, 2013.
30. Watkins KD, Boettger RF, Hanger KM, et al. Use of sublingual tacrolimus in lung transplant recipients. J Heart Lung Transplant 2012;31:127-32.
31. Knoop C, Thiry P, Saint-Marcoux F, et al. Tacrolimus pharmacokinetics and dose monitoring after lung transplantation for cystic fibrosis and other conditions. Am J Transplant 2005;5:1477-82.
32. Ragette R, Kamler M, Weinreich G, et al. Tacrolimus pharmacokinetics in lung transplantation: new strategies for monitoring. J Heart Lung Transplant 2005;24:1315-9.
33. Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant 2008;22:1-15.
34. Heisel O, Heisel R, Balshaw R, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant 2004;4:583-95.
35. McAlister VC, Haddad E, Renouf E, et al. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant 2006;6:1578-85.
36. Moore R, Hernandez D, Valantine H. Calcineurin inhibitors and post-transplant hyperlipidaemias. Drug Saf 2001;24:755-66.
37. Penninga L, Møller CH, Gustafsson F, et al. Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials.Eur J Clin Pharmacol 2010;66:1177-87.
38. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007;7:1506-14.
39. White M, Haddad H, Leblanc MH, et al. Conversion from cyclosporine microemulsion to tacrolimus-based immunoprophylaxis improves cholesterol profile in heart transplant recipients with treated but persistent dyslipidemia: the Canadian multicentre randomized trial of tacrolimus vs cyclosporine microemulsion. J Heart Lung Transplant 2005;24:798-809.
40. Taylor JL, Palmer SM. Critical care perspective on immunotherapy in lung transplantation. J Intensive Care Med 2006;21:327-44.
41. Griffith BP, Bando K, Hardesty RL, et al. A prospective randomized trial of FK506 versus cyclosporine after human pulmonary transplantation. Transplantation 1994;57:848-51.
42. Treede H, Klepetko W, Reichenspurner H, et al. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. J Heart Lung Transplant 2001;20:511-7.
43. Zuckermann A, Reichenspurner H, Birsan T, et al. Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. J Thorac Cardiovasc Surg 2003;125:891-900.
44. Hachem RR, Yusen RD, Chakinala MM, et al. A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. J Heart Lung Transplant 2007;26:1012-8.
45. Neurohr C, Huppmann P, Zimmermann G, et al. Tacrolimus and mycophenolate mofetil as first line immunosuppression after lung transplantation. Transpl Int 2009;22:635-43.
46. Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant 2012;31:797-804.
47. Taylor AL, Watson CJ, Bradley JA. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. Crit Rev Oncol Hematol 2005;56:23-46.
48. Holt DW. Monitoring mycophenolic acid. Ann Clin Biochem 2002;39:173-83.
49. Hale MD, Nicholls AJ, Bullingham RE, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin

Pharmacol Ther 1998;64:672-83.
50. Knoop C, Haverich A, Fischer S. Immunosuppressive therapy after human lung transplantation. Eur Respir J 2004;23:159-71.
51. Ting LS, Partovi N, Levy RD, et al. Limited sampling strategy for predicting area under the concentration-time curve of mycophenolic acid in adult lung transplant recipients. Pharmacotherapy 2006;26:1232-40.
52. Whyte RI, Rossi SJ, Mulligan MS, et al. Mycophenolate mofetil for obliterative bronchiolitis syndrome after lung transplantation. Ann Thorac Surg 1997;64:945-8.
53. Palmer SM, Baz MA, Sanders L, et al. Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. Transplantation 2001;71:1772-6.
54. McNeil K, Glanville AR, Wahlers T, et al. Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation 2006;81:998-1003.
55. Roman A, Ussetti P, Zurbano F, et al. A retrospective 12-month study of conversion to everolimus in lung transplant recipients. Transplant Proc 2011;43:2693-8.
56. Cahill BC, Somerville KT, Crompton JA, et al. Early experience with sirolimus in lung transplant recipients with chronic allograft rejection. J Heart Lung Transplant 2003;22:169-76.
57. Parada MT, Alba A, Sepúlveda C, et al. Long-term use of everolimus in lung transplant patients. Transplant Proc 2011;43:2313-5.
58. Shitrit D, Rahamimov R, Gidon S, et al. Use of sirolimus and low-dose calcineurin inhibitor in lung transplant recipients with renal impairment: results of a controlled pilot study. Kidney Int 2005;67:1471-5.
59. Gullestad L, Iversen M, Mortensen SA, et al. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. Transplantation 2010;89:864-72.
60. Azzola A, Havryk A, Chhajed P, et al. Everolimus and mycophenolate mofetil are potent inhibitors of fibroblast proliferation after lung transplantation. Transplantation 2004;77:275-80.
61. Hernández RL, Gil PU, Gallo CG, et al. Rapamycin in lung transplantation. Transplant Proc 2005 Nov;37:3999-4000.
62. Villanueva J, Boukhamseen A, Bhorade SM. Successful use in lung transplantation of an immunosuppressive regimen aimed at reducing target blood levels of sirolimus and tacrolimus. J Heart Lung Transplant 2005;24:421-5.
63. Groetzner J, Kur F, Spelsberg F, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. J Heart Lung Transplant 2004;23:632-8.
64. King-Biggs MB, Dunitz JM, Park SJ, et al. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation 2003;75:1437-43.
65. Snell GI, Valentine VG, Vitulo P, et al. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. Am J Transplant 2006;6:169-77.
66. Sacher VY, Fertel D, Srivastava K, et al. Effects of prophylactic use of sirolimus on bronchiolitis obliterans syndrome development in lung transplant recipients. Ann Thorac Surg 2014;97:268-74.
67. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharmacol 2006;148:245-54.
68. Borro JM, Solé A, De la Torre M, et al. Steroid withdrawal in lung transplant recipients. Transplant Proc 2005;37:3991-3.
69. Shitrit D, Bendayan D, Sulkes J, et al. Successful steroid withdrawal in lung transplant recipients: result of a pilot study. Respir Med 2005;99:596-601.
70. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 2007;26:1229-42.
71. Berry G, Burke M, Andersen C, et al. Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT. J Heart Lung Transplant 2013;32:14-21.
72. Glanville AR. Antibody-mediated rejection in lung transplantation: myth or reality? J Heart Lung Transplant 2010;29:395-400.
73. Appel JZ 3rd, Hartwig MG, Davis RD, et al. Utility of peritransplant and rescue intravenous immunoglobulin and extracorporeal immunoadsorption in lung transplant recipients sensitized to HLA antigens. Hum Immunol 2005;66:378-86.
74. Hachem RR, Yusen RD, Meyers BF, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. J Heart Lung Transplant 2010;29:973-80.
75. Astor TL, Weill D, Cool C, et al. Pulmonary capillaritis in lung transplant recipients: treatment and effect on allograft

function. J Heart Lung Transplant 2005;24:2091-7.
76. Baum C, Reichenspurner H, Deuse T. Bortezomib rescue therapy in a patient with recurrent antibody-mediated rejection after lung transplantation. J Heart Lung Transplant 2013;32:1270-1.
77. Neumann J, Tarrasconi H, Bortolotto A, et al. Acute humoral rejection in a lung recipient: reversion with bortezomib. Transplantation 2010;89:125-6.
78. Hachem R. Antibody-Mediated Lung Transplant Rejection. Curr Respir Care Rep 2012;1:157-61.
79. Bittner HB, Dunitz J, Hertz M, et al. Hyperacute rejection in single lung transplantation--case report of successful management by means of plasmapheresis and antithymocyte globulin treatment. Transplantation 2001;71:649-51.
80. Dawson KL, Parulekar A, Seethamraju H. Treatment of hyperacute antibody-mediated lung allograft rejection with eculizumab. J Heart Lung Transplant 2012;31:1325-6.
81. Iacono AT, Keenan RJ, Duncan SR, et al. Aerosolized cyclosporine in lung recipients with refractory chronic rejection. Am J Respir Crit Care Med 1996;153:1451-5.
82. Iacono AT, Smaldone GC, Keenan RJ, et al. Dose-related reversal of acute lung rejection by aerosolized cyclosporine. Am J Respir Crit Care Med 1997;155:1690-8.
83. Iacono AT, Corcoran TE, Griffith BP, et al. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. Eur Respir J 2004;23:384-90.
84. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med. 2006;354:141-50.
85. Watts AB, Cline AM, Saad AR, et al. Characterization and pharmacokinetic analysis of tacrolimus dispersion for nebulization in a lung transplanted rodent model. Int J Pharm 2010;384:46-52.
86. Watts AB, Peters JI, Talbert RL, et al. Preclinical evaluation of tacrolimus colloidal dispersion for inhalation. Eur J Pharm Biopharm 2011;77:207-15.
87. Bayer J, Das NA, Baisden CE, et al. Effect of inhaled tacrolimus on ischemia reperfusion injury in rat lung transplant model. J Thorac Cardiovasc Surg 2013;146:1213-9; discussion 1219.
88. Hayes D Jr, Zwischenberger JB, Mansour HM. Aerosolized tacrolimus: a case report in a lung transplant recipient. Transplant Proc 2010;42:3876-9.
89. Vos R, Vanaudenaerde BM, Verleden SE, et al. Anti-inflammatory and immunomodulatory properties of azithromycin involved in treatment and prevention of chronic lung allograft rejection. Transplantation 2012;94:101-9.
90. Jaffé A, Francis J, Rosenthal M, et al. Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet 1998;351:420.
91. Wolter J, Seeney S, Bell S, et al. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax 2002;57:212-6.
92. Gerhardt SG, McDyer JF, Girgis RE, et al. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. Am J Respir Crit Care Med 2003;168:121-5.
93. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2004;77:1465-7.
94. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2005;172:772-5.
95. Gottlieb J, Szangolies J, Koehnlein T, et al. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2008;85:36-41.
96. Porhownik NR, Batobara W, Kepron W, et al. Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. Can Respir J 2008;15:199-202.
97. Vos R, Vanaudenaerde BM, Ottevaere A, et al. Long-term azithromycin therapy for bronchiolitis obliterans syndrome: divide and conquer? J Heart Lung Transplant 2010;29:1358-68.
98. Verleden GM, Vanaudenaerde BM, Dupont LJ, et al. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2006;174:566-70.
99. Federica M, Nadia S, Monica M, et al. Clinical and immunological evaluation of 12-month azithromycin therapy in chronic lung allograft rejection. Clin Transplant 2011;25:E381-9.
100. Jain R, Hachem RR, Morrell MR, et al. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. J Heart Lung Transplant 2010;29:531-7.
101. Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. Eur Respir J 2011;37:164-72.
102. Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant

2010;29:424-31.
103. Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant 2012;31:950-7.
104. Greer M, Dierich M, De Wall C, et al. Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. Am J Transplant 2013;13:911-8.
105. Ropponen JO, Syrjälä SO, Hollmén M, et al. Effect of simvastatin on development of obliterative airway disease: an experimental study. J Heart Lung Transplant 2012;31:194-203.
106. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4+CD25+ T cells. Atherosclerosis 2008;197:829-39.
107. Kwak B, Mulhaupt F, Myit S, et al. Statins as a newly recognized type of immunomodulator. Nat Med 2000;6:1399-402.
108. Watts KL, Sampson EM, Schultz GS, et al. Simvastatin inhibits growth factor expression and modulates profibrogenic markers in lung fibroblasts. Am J Respir Cell Mol Biol 2005;32:290-300.
109. Johnson BA, Iacono AT, Zeevi A, et al. Statin use is associated with improved function and survival of lung allografts. Am J Respir Crit Care Med 2003;167:1271-8.
110. Li Y, Gottlieb J, Ma D, et al. Graft-protective effects of the HMG-CoA reductase inhibitor pravastatin after lung transplantation--a propensity score analysis with 23 years of follow-up. Transplantation 2011;92:486-92.
111. Margolin SB. eds. Investigation of new drug: pirfenidone. Dallas, TX: Marnac, Inc, 2002.
112. Dosanjh AK, Wan B, Throndset W, et al. Pirfenidone: a novel antifibrotic agent with implications for the treatment of obliterative bronchiolitis. Transplant Proc 1998;30:1910-1.
113. Zhou H, Latham CW, Zander DS, et al. Pirfenidone inhibits obliterative airway disease in mouse tracheal allografts. J Heart Lung Transplant 2005;24:1577-85.
114. Visner GA, Liu F, Bizargity P, et al. Pirfenidone inhibits T-cell activation, proliferation, cytokine and chemokine production, and host alloresponses. Transplantation 2009;88:330-8.
115. Bizargity P, Liu K, Wang L, et al. Inhibitory effects of pirfenidone on dendritic cells and lung allograft rejection. Transplantation 2012;94:114-22.
116. Ihle F, von Wulffen W, Neurohr C. Pirfenidone: a potential therapy for progressive lung allograft dysfunction? J Heart Lung Transplant 2013;32:574-5.
117. Vos R, Verleden SE, Ruttens D, et al. Pirfenidone: a potential new therapy for restrictive allograft syndrome? Am J Transplant 2013;13:3035-40.

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Review Article

Ex vivo lung perfusion

Tiago N. Machuca, Marcelo Cypel

Toronto Lung Transplant Program, University of Toronto, University Health Network, Toronto, Ontario, Canada

Correspondence to: Marcelo Cypel, MD. Toronto Lung Transplant Program, Toronto General Hospital, 200 Elizabeth St, 9N946, Toronto, Ontario, M5G 2C4 Canada. Email: marcelo.cypel@uhn.ca.

Abstract: Lung transplantation (LTx) is an established treatment option for eligible patients with end-stage lung disease. Nevertheless, the imbalance between suitable donor lungs available and the increasing number of patients considered for LTx reflects in considerable waitlist mortality. Among potential alternatives to address this issue, ex vivo lung perfusion (EVLP) has emerged as a modern preservation technique that allows for more accurate lung assessment and also improvement of lung function. Its application in high-risk donor lungs has been successful and resulted in safe expansion of the donor pool. This article will: (I) review the technical details of EVLP; (II) the rationale behind the method; (III) report the worldwide clinical experience with the EVLP, including the Toronto technique and others; (IV) finally, discuss the growing literature on EVLP application for donation after cardiac death (DCD) lungs.

Keywords: Ex vivo lung perfusion (EVLP); lung transplantation; organ preservation

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The shortage of donor lungs

According to the *Thirtieth Adult Lung and Heart-Lung Transplant Report 2013*, from the Registry of the International Society for Heart and Lung Transplantation, lung transplantation (LTx) is a therapy that is being performed worldwide, with numbers increasing every year (1). In 2011, 3,640 LTxs were reported compared to only 1,712 annual cases a decade ago. As the outcomes tend to improve, an increasing number of patients with end-stage lung disease are being considered for LTx. Nevertheless, the amount of lungs suitable for transplantation has not followed this trend and this equation generates considerable waitlist mortality (15.4 per 100 wait-list years in the US form 2010 to 2012) (2).

Donor lungs are subjected to several injurious mechanisms during the brain death/organ donation process (such as ventilator-acquired pneumonia, neurogenic and hydrostatic pulmonary edema, barotrauma). Thus, it is not surprising that the majority of donor lungs are not utilized for transplantation (39% Eurotransplant 2012, 78% SRTR in the US 2012).

Strategies for lung donor pool expansion

Expansion of the donor pool has been attempted by extending the donor selection conventional criteria, by use of donation after cardiac death (DCD) and, lastly, with the implementation of ex vivo lung perfusion (EVLP). The ideal donor corresponds to a <55 year-old with <20 pack-year smoking history, no chest trauma, clear chest X-ray, P/F >300 and absence of purulent secretions and organisms on gram stain of respiratory samples. This scenario is known to correspond to less than half of the donors utilized for transplantation (3). Several studies addressing the use of extended criteria donors have been published and, more recently, a review study summarized the findings of 10 studies ranging from 1993 to 2010, bringing the best evidence up to date (4). Although no clear differences in mid or long-term survival were observed, 4 of these studies revealed worse early outcomes (such as 30- and 90-day mortality, ICU and hospital stay and gas exchange at ICU arrival). Recently, the Hannover group has shown an interesting algorithm proposing allocation of extended criteria donor lungs to lower-risk recipients. Results were

encouraging and deserve further analysis (5).

Although the first successful LTx was performed from DCD, the concept of using controlled DCD lungs has been clinically revisited by D'Alessandro *et al.*, in 1995 (6). Series of studies have followed, reporting an increasing international experience and highlighting the potential of DCD to partially address the shortage of donor lungs (7-13). Nevertheless, caution is still observed in the transplant community as there are a series of specific injuries that the DCD lung is prone to, specially during the interval from withdrawal of life sustaining therapies to pulmonary artery (PA) flush. Another potential source of lungs comes from the use of uncontrolled DCDs (Maastricht categories I and II). The group of Madrid has explored this peculiar pool, reporting the experience with 29 cases. Ninety-day and 1-year mortality were 22% and 32% respectively, with higher rates of primary graft dysfunction (PGD) 2-3 than expected (14).

The use of lungs from smoker donors has been recently studied in a large registry database including 1,295 transplants (510 with smoking history) from UK. Despite presenting worse 3-year survival, the use of lungs from donors with a positive smoking history was shown to provide a survival benefit for patients with interstitial lung disease listed for transplantation (15). Several recent studies followed and supported the use of such donors (16-18). Nevertheless, caution was raised in the analysis of the UNOS database including 3,704 single-lung transplants from 2005 to 2011. In this modality of transplant, recipients from donors with an active smoking history, but not those from donors that quit smoking, were associated with increased mortality (19).

Lastly, clinical EVLP was shown to safely increase the donor pool by preserving high-risk donor lungs with similar outcomes to standard criteria donor lungs (20). This review will focus on technical aspects of EVLP, its recent clinical experience and pre-clinical application in DCD.

EX vivo lung perfusion

Perfusion of whole organs was initially envisioned by Alexis Carrel and Charles Lindbergh. In the 30's, they performed several experiments with organs such as heart, kidney, thyroid, ovary, adrenal glands and spleen (21). Up to the 90's, experiments with lung perfusion were viewed as a reliable method to study pulmonary physiology. The first clinical application was described by Steen and coworkers at University Hospital of Lund. In 2001, they described the utilization of EVLP to assess the lungs of a 54-year-old who suffered a myocardial infarction while admitted to the intensive care unit. Lungs were topically cooled with perfadex and procured after 190 minutes of cardiopulmonary resuscitation cessation. EVLP was performed for 65 minutes and a successful right single lung transplant was performed (22). The same group further expanded the application of short-period EVLP to lungs initially rejected for transplantation. A total of 6 sets of donor lungs were perfused from 61 to 121 minutes, rendering six successful double lung transplants (23). The Toronto group mastered the technique and introduced the concept of extended EVLP, focusing not only on reassessment but also on providing a platform for treatment delivery in the normothermic state (24,25).

EVLP—the Toronto technique

The foundations of our current technique for clinical EVLP are: (I) gradual rewarming up to normothermia; (II) gradual increase in vascular flow as the lungs are rewarmed, targeting 40% of the donor predicted cardiac output; (III) protective lung ventilation; (IV) acellular perfusate with increased colloid osmotic pressure.

The indications for EVLP are listed in *Table 1*. Once at the transplant center, the lungs are dissected on the back table. The left atrial (LA) cuff is trimmed and sewn to a dedicated cannula with two 4-0 polypropylene running sutures (*Figure 1*). If adequate length on the PA is available, the PA cannula can be simply inserted proximal to its bifurcation and secured with two heavy silk ties (*Figure 2*). In cases of short main PA—usually in concomitant heart procurement—a cuffed PA cannula can be sewn with two 5-0 polypropylene running sutures, similarly to the atrium. With the trachea clamped at the level of the carina, the staple line is opened and a conventional endotracheal tube is inserted and secured with two heavy silk ties (*Figure 3*). A second retrograde flush with 1L of Perfadex is performed. The inflated lungs are then taken to the EVLP dome and ready to be connected to the circuit (*Figure 4*). If one of the lungs is judged too damaged for clinical EVLP (e.g., due to pneumonia), the contralateral lung can be perfused alone. Care should be taken to keep adequate arterial and atrial cuffs and a long trachea/bronchus at the moment of division.

The EVLP circuit

A dedicated circuit composed of a centrifugal pump, a

Table 1 Current indications for EVLP for both brain death donors and donors after cardiac death (20,26)

- Best PaO_2/FiO_2 <300 mmHg
- Signs of pulmonary edema either on chest X-ray or physical examination at the donor site
- Poor lung compliance during examination at procurement operation
- High-risk history, such as >10 units of blood transfusion or questionable history of aspiration
- DCDs with >60 min interval from withdrawal life support to cardiac arrest interval

EVLP, ex vivo lung perfusion; DCD, donation after cardiac death.

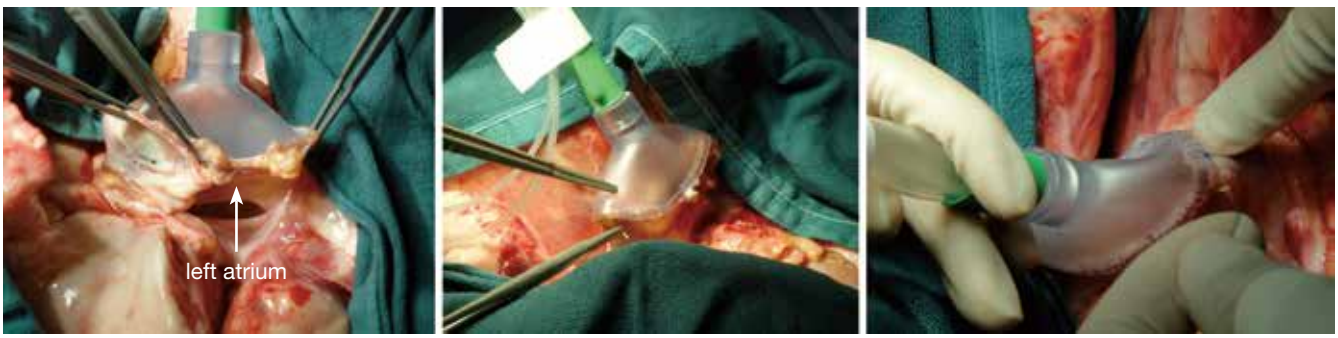

Figure 1 Preparation of the left atrium.

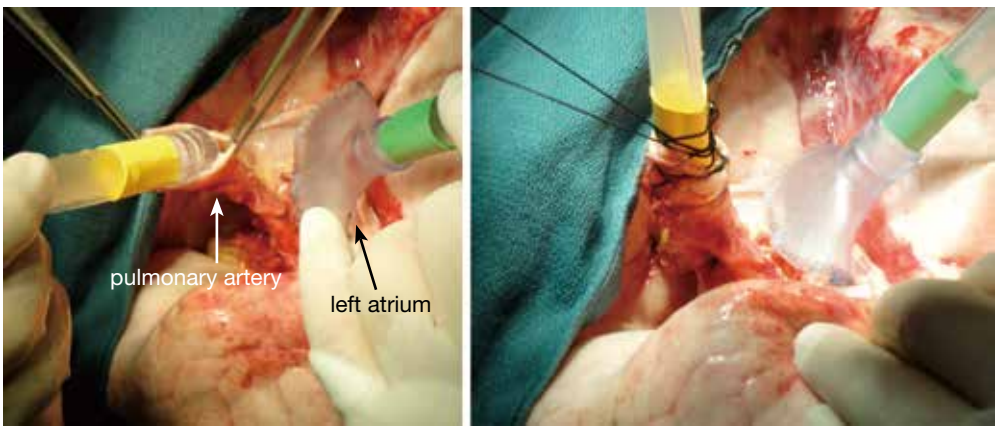

Figure 2 Preparation of the pulmonary artery.

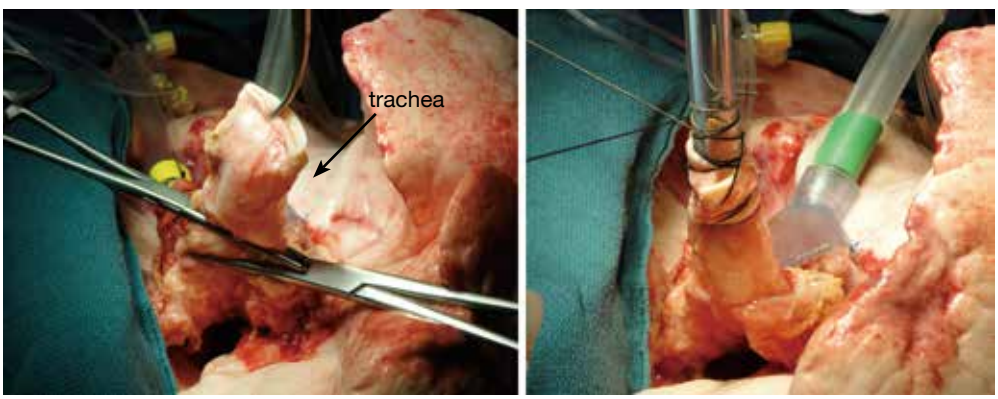

Figure 3 Preparation of the trachea.

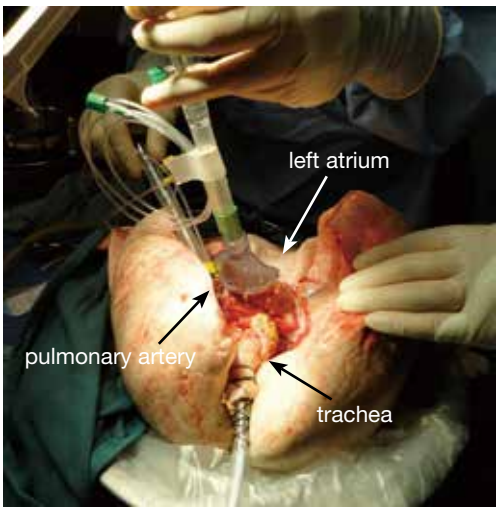

Figure 4 Lungs after cannulation.

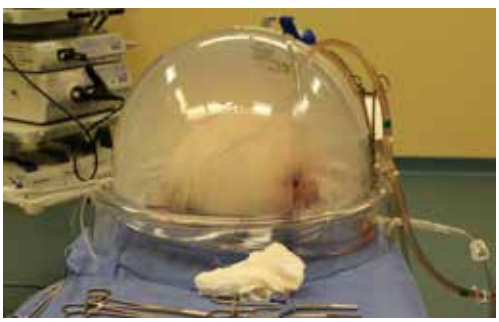

Figure 5 Lungs being ventilated and perfused on steady-state.

leukocyte filter, a hollow-fiber oxygenator heat exchanger and a hardshell reservoir is currently used. It is primed with 2.0 L of Steen solution (XVIVO, Vitrolife), 500 mg methylprednisolone (Solu-medrol; Sandoz Canada, Boucherville, Canada), 3,000 IU of unfractionated heparin (Organon, Canada) and antibiotic (500 mg imipenem/cilastatin, Primaxin; Merck, Whitehouse Station, NJ).

Initiation and steady state

Once on the EVLP dome, a cotton sponge is positioned beneath the lung block to prevent excessive sliding. Antegrade flow is commenced through the PA cannula, which is attached to the circuit once appropriate deairing is achieved. The LA cannula is then deaired and connected to the circuit. The outflow clamp is now removed. Our target perfusion flow consists of 40% of the donor predicted cardiac output. Following our principles of gradual rewarming and stepwise increase in vascular flow, the procedure is then initiated with lungs on room temperature and perfusion with 10% of the calculated target flow. At 10 minutes, the flow is raised to 20% of predicted and the temperature is set to 30 ℃. At subsequent 10-minute time points (20, 30, 40 and 50 minutes), the flow is increased to 30%, 50%, 80% and finally 100% of target, respectively. Furthermore, the temperature is set to 37 ℃ at 20 minutes and ventilation is initiated (7 mL/kg, PEEP 5 cm H_2O and 7 cycles/min) when the temperature reaches 33 ℃. Once the lungs are being ventilated, the gas mixture (86% N_2, 8% CO_2 and 6% O_2) is turned on at a sweep of 1 L/min. The target of a post-membrane pCO_2 between 35-40 mmHg is achieved by titrating the sweep gas. Lastly, the left atrial pressure should be carefully maintained in the 3-5 mmHg range by adjusting the level of the reservoir. Once the lungs are normothermic, ventilated and target flow is achieved, recruitment maneuvers are performed up to 25 cm H_2O. The lungs have now reached the steady state (*Figure 5*). Steen solution is exchanged from the circuit hourly, 500 mL in the first hour followed by 250 mL thereafter.

Assessment mode

Assessment is performed hourly. Ventilation parameters are set to 10 mL/kg tidal volume, 10 breaths per minute and FiO_2 1.0 for five minutes. PA pressure, LA pressure, peak airway pressure, plateau pressure, dynamic and static compliance are recorded. Perfusate gas analysis is done in samples taken from the venous and arterial sides. At 1 hour of EVLP and then every two hours, a lung X-ray is routinely performed. Criteria for lung acceptance or declination for transplantation after EVLP are displayed in *Table 2*. One should notice that the acellular nature of the Steen solution makes perfusate pO_2 a later marker of lung injury. As demonstrated by Yeung and coworkers, compliance and peak airway pressure deterioration are observed before changes in perfusate pO_2 (27). Pulmonary recruitment is performed every 30 minutes after each assessment by increasing the tidal volume with subsequent inspiratory hold maneuvers up to 25 cm H_2O for ten seconds.

Termination of perfusion

Our clinical protocol includes EVLP for four to six hours. Frequently, it is possible to make the decision at three hours (3 assessments, 2 lung X-rays) and send for the recipient. By

Table 2 Acceptance and exclusion criteria after 4-6 hours of clinical EVLP (20,26)

Acceptance criteria after EVLP
P/F ratio >400 mmHg
Stable or improving pulmonary artery pressure
Stable or improving airway pressure
Stable or improving pulmonary compliance
Exclusion criteria after EVLP
P/F ratio <400 mmHg
Greater than 15% deterioration on pulmonary artery pressure
Greater than 15% deterioration on airway pressure/compliance

EVLP, ex vivo lung perfusion.

the fourth hour the recipient will be relatively ready for skin incision. Nevertheless, if no clear decision can be made at this time point, perfusion can be extended for up to 6 hours.

Once decision is made to terminate perfusion, lungs are ventilated with 0.5 FiO_2 and cooled to 15 ℃. The inflow and outflow cannulae are clamped and cut. The endotracheal tube is clamped as well with special attention to maintain the lungs inflated. A last antegrade flush is performed with 500 mL of Steen solution. The vascular cannulae are removed and the trachea is stapled just below the endotracheal tube. Topical cooling with Perfadex and ice follows the same steps of conventional preservation and the lungs are taken to the recipient OR inside a cooler.

Worldwide experience with clinical EVLP

The Toronto technique

The Toronto Lung Transplant Program conducted a nonrandomized clinical trial to assess the feasibility of EVLP selecting high-risk donor lungs for this modality of preservation (20). A total of 23 donor lungs were submitted to EVLP with 20 being ultimately transplanted (15 bilateral and 5 unilateral lung transplants). The primary end-point of the study (PGD grade 2 or 3 at 72 hours) was recorded in 15% of the EVLP group and 30% of the contemporary no EVLP controls (116 cases), with no significant difference. Secondary end-points such as PGD 2 or 3 at ICU arrival, 24 and 48 hours; ECLS requirement; days on mechanical ventilation; ICU stay; hospital stay and 30-day mortality were also comparable between groups. This experience was recently updated with a total of 50 lung transplants from 58 EVLPs (86% yield) (26). In the study period, from September 2008 to December 2011, 253 lung transplants were performed with conventional preservation lungs. PGD 3 at 72 hours was recorded in 2% EVLP *vs.* 8.5% control (P=0.14). Again, time on mechanical ventilation, ECLS requirement, ICU stay, hospital stay and 30-day mortality were not different. Furthermore, similar 1-year survivals were observed: 87% for EVLP group *vs.* 86% for the standard group.

In 2012, the group from Vienna reported their experience with 13 clinical EVLPs which rendered nine double-lung transplants (69% yield) (28). Early outcomes such as days on mechanical ventilation, ICU stay, hospital stay and 30-day mortality were comparable to 119 contemporary conventional preservation transplants. Of notice, some modifications from the Toronto technique were implemented: (I) decision was made at two hours of perfusion if physiologic parameters were met; (II) recruitment maneuvers were performed 10 minutes before assessments (as opposed to 30 minutes); (III) lungs were ventilated for 15 minutes on 1.0 FiO_2 for each assessment (as opposed to five minutes). Interestingly, all the four declined cases developed massive pulmonary edema and were recovered from donors with trauma history.

The groups from Toronto, Vienna and Paris presented their clinical EVLP experience at the 2013 ISHLT meeting (29). A total of 125 clinical EVLPs were performed with an 82.5% yield. Similarly to previous uni-institutional reports, the incidence of PGD3 at 72 hours was 5% and the 12-month mortality was 12%.

In 2012, the Harefield Hospital (UK) reported six double lung transplants generated from 13 EVLPs (yield 46%) (30). Although the median requirement of mechanical ventilation post-transplant was greater than seven days, all patients ultimately left the hospital and were alive at three months. The Toronto technique was implemented with some

modifications, such as shorter perfusion times (average 2 hours) and no interval lung X-ray in 50% of the accepted cases.

The group of Torino described nine EVLPs rendering seven lung transplants (yield 78%) (31). These cases corresponded to 30% of their LTx activity and illustrated the impact of EVLP on lower volume centers.

In the Newcastle experience with 6 lung transplants from 18 EVLPs (yield 33%), all patients survived to hospital discharge (32). Furthermore, this report pointed to a possible benefit of EVLP: bacterial loads in bronchoalveolar lavages at the end of EVLP were significantly lower than on samples taken at its initiation. Authors also reported that, despite decrease in the bacterial loads there was an increase in the load of *Candida sp.* in two of their first three cases. After this observation, Amphotericin B was routinely added to the perfusate. Further studies are required to better elucidate the role of anti-fungal therapy in EVLP.

The NOVEL Lung trial is an FDA mandated multicenter clinical trial (NOVEL Lung Trial) studying EVLP for marginal donors. The initial report included 31 patients that received EVLP lungs. Early outcomes such as PGD, length on mechanical ventilation, ICU stay, hospital stay and 30-day mortality were similar to 31 non-EVLP controls (33). At the 2014 ISHLT meeting, the trial results were updated to 76 EVLPs rendering 42 lung transplants (55% conversion rate) (34). In comparison with 42 contemporary controls, early outcomes and 1-year survival were not different.

The Lund technique

The main differences from the Toronto technique reside in the open left atrium, the use of Steen solution mixed with red blood cells and the perfusion at flows correspondent to 100% of the donor predicted cardiac output (35).

Following the successful case in 2001 (22), Steen and coworkers reported the use of EVLP for the evaluation of 9 donors lungs rejected for transplantation (23). Ultimately, 6 double lung transplants were performed, representing 35% of the lung transplant activity for the study period. Although two patients died early on the post-transplant course (one 63-year-old COPD male died at 95 days due to sepsis and multi-organ dysfunction; one 64-year-old COPD female died at 9 months due to rejection); the remaining four were followed for almost 2 years and presented good lung function.

The group from University of Gothenburg has reported their outcomes with 11 EVLPs over an 18-month period (36). A total of eight double and three single LTxs were performed and, although hospital stays were similar, the time on mechanical ventilation and ICU length of stay were longer in the EVLP group compared to conventional transplants. Nevertheless, there was no hospital mortality in the EVLP group.

Reflecting the widepread utilization of EVLP by LTx programs throughout the world, the group from Copenhagen recently reported the Danish experience with 7 EVLP lung transplants (37). This number corresponded to 21% of the yearly activity and the outcomes were favorable despite one death at 104 days post-transplant due to *Mycobacterium abscessus* infection.

The portable *ex vivo* technique

This system is capable of transportation in addition to ventilation/perfusion. Similarly to the Lund technique, the left atrium is kept open and red blood cells are added to the perfusate (a modified low-potassium dextran solution). The perfusion flow is set to 2.5 L/min (38).

A pilot study assessing preservation and transportation of conventional criteria donor lungs was published in 2012 by the programs of Hannover and Madrid (38). A total of 12 patients were transplanted, with perfusion times ranging from 188 to 622 minutes. All cases were bilateral LTxs and there was no PGD 3 at 72 hours. Currently there is an ongoing multicentre clinical trial assessing the feasibility and potential benefits of this strategy for extended criteria donor lungs.

EVLP as a platform for assessment and treatment of DCD lungs

There is a growing body of research focusing on the application of EVLP to assess and repair DCD lungs. The low clinical utilization rates of these lungs are likely driven by the different injuries (such as warm ischemia, hypoxia, hypotension and aspiration) that they are prone when compared to neurological determination of death donors (39). The potential of EVLP to further refine DCD lung selection is well illustrated by the pre-clinical report of Sanchez *et al.*, showing that improved endothelial function reflected in better EVLP physiological performance in porcine lungs treated with pre-arrest heparinization (40).

Furthermore, the use of EVLP as a platform to deliver

different medications has been tested and proved to be beneficial in most reports. Nakajima and coworkers have added nitroglycerin and dibutyryl cyclic adenosine monophosphate to Steen solution during EVLP of lungs submitted to 4 hours of warm ischemia (41). After single LTx, EVLP lungs had better function, lower histological signs of acute lung injury and improved microvascular patency compared to conventional preservation lungs. Mulloy and coworkers (42) added a selective adenosine 2A agonist to the perfusate in a model of one hour of warm ischemia in pigs. After procurement, lungs submitted to extra four hours of cold ischemia and then four hours of EVLP performed significantly better than lungs submitted to four hours of cold ischemia only, with less histological lung injury and lower levels of inflammatory cytokines in the bronchoalveolar lavage after single left LTx.

Lastly, some groups have moved further with the clinical use of uncontrolled DCDs. Pioneer work from the Hospital Universitario Puerta de Hierro has initially shown high incidence of PGD3 (38%), with 17% hospital mortality and 57% 1-year survival from 29 uncontrolled DCD LTxs (43). The addition of EVLP to this algorithm helped to better select this lungs and rendered no case of PGD3 in the initial 4 EVLP LTxs, with additional exclusion of four lungs with poor EVLP performance (44). More recently, Tom Egan has shown the feasibility of a similar approach in a US clinical trial, having procured and perfused two uncontrolled DCD lungs. Although one of them deteriorated on the circuit, the other one presented adequate function and was not transplanted only because there was no recipient to match blood type and size (45).

The future

The current EVLP assessment is mainly based on physiological parameters, added to lung X-ray, bronchoscopy and macroscopic evaluation. Although EVLP has provided similar results of LTx with extended criteria donor lungs compared to those with conventional ones, we still observe a small percentage of PGD3. Certainly one cannot control for recipient factors, nevertheless, the addition of biomarkers to EVLP assessment has the potential to further refine donor lung selection. Since plausible biomarker candidates have been suggested, the next barrier to clinical translation resides in the design of rapid diagnostic assays in order not only to validate but also to provide this information in a timely fashion.

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References

1. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
2. Valapour M, Paulson K, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: lung. Am J Transplant 2013;13 Suppl 1:149-77.
3. Pierre AF, Sekine Y, Hutcheon MA, et al. Marginal donor lungs: a reassessment. J Thorac Cardiovasc Surg. 2002;123:421-7; discussion, 427-8.
4. Schiavon M, Falcoz PE, Santelmo N, et al. Does the use of extended criteria donors influence early and long-term results of lung transplantation? Interact Cardiovasc Thorac Surg 2012;14:183-7.
5. Sommer W, Kühn C, Tudorache I, et al. Extended criteria donor lungs and clinical outcome: results of an alternative allocation algorithm. J Heart Lung Transplant 2013;32:1065-72.
6. D'Alessandro AM, Hoffmann RM, Knechtle SJ, et al. Successful extrarenal transplantation from non-heart-beating donors. Transplantation 1995;59:977-82.
7. Cypel M, Sato M, Yildirim E, et al. Initial experience with lung donation after cardiocirculatory death in Canada. J Heart Lung Transplant 2009;28:753-8.
8. Erasmus ME, Verschuuren EA, Nijkamp DM, et al. Lung transplantation from nonheparinized category III non-heart-beating donors. A single-centre report. Transplantation 2010;89:452-7.
9. Love RB. Perspectives on lung transplantation and donation-after-determination-of-cardiac-death donors. Am J Transplant 2012;12:2271-2.
10. Mason DP, Brown CR, Murthy SC, et al. Growing single-center experience with lung transplantation using donation after cardiac death. Ann Thorac Surg 2012;94:406-11; discussion 411-2.
11. De Oliveira NC, Osaki S, Maloney JD, et al. Lung transplantation with donation after cardiac death

donors: long-term follow-up in a single center. J Thorac Cardiovasc Surg 2010;139:1306-15.
12. Levvey BJ, Harkess M, Hopkins P, et al. Excellent clinical outcomes from a national donation-after-determination-of-cardiac-death lung transplantcollaborative. Am J Transplant 2012;12:2406-13.
13. Puri V, Scavuzzo M, Guthrie T, et al. Lung transplantation and donation after cardiac death: a single center experience. Ann Thorac Surg 2009;88:1609-14; discussion 1614-5.
14. de Antonio DG, Marcos R, Laporta R, et al. Results of clinical lung transplant from uncontrolled non-heart-beating donors. J Heart Lung Transplant 2007;26:529-34.
15. Bonser RS, Taylor R, Collett D, et al. Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. Lancet 2012;380:747-55.
16. Sabashnikov A, Patil NP, Mohite PN, et al. Influence of donor smoking on midterm outcomes after lung transplantation. Ann Thorac Surg 2014;97:1015-21.
17. Shigemura N, Toyoda Y, Bhama JK, et al. Donor smoking history and age in lung transplantation: a revisit. Transplantation 2013;95:513-8.
18. Taghavi S, Jayarajan S, Komaroff E, et al. Double-lung transplantation can be safely performed using donors with heavy smoking history. Ann Thorac Surg 2013;95:1912-7; discussion 1917-8.
19. Taghavi S, Jayarajan SN, Komaroff E, et al. Single-lung transplantation can be performed with acceptable outcomes using selected donors with heavysmoking history. J Heart Lung Transplant 2013;32:1005-12.
20. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364:1431-40.
21. Carrel A, Lindbergh CA. The culture of whole organs. Science 1935;81:621-3.
22. Steen S, Sjöberg T, Pierre L, et al. Transplantation of lungs from a non-heart-beating donor. Lancet 2001;357:825-9.
23. Ingemansson R, Eyjolfsson A, Mared L, et al. Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. Ann Thorac Surg 2009;87:255-60.
24. Cypel M, Rubacha M, Yeung J, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. Am J Transplant 2009;9:2262-9.
25. Cypel M, Yeung JC, Hirayama S, et al. Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant 2008;27:1319-25.
26. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg 2012;144:1200-6.
27. Yeung JC, Cypel M, Machuca TN, et al. Physiologic assessment of the ex vivo donor lung for transplantation. J Heart Lung Transplant 2012;31:1120-6.
28. Aigner C, Slama A, Hötzenecker K, et al. Clinical ex vivo lung perfusion--pushing the limits. Am J Transplant 2012;12:1839-47.
29. Cypel M, Aigner C, Sage E, et al. Three center experience with clinical normothermic Ex Vivo lung perfusion. The Journal of Heart and Lung Transplantation 2013;32:S16.
30. Zych B, Popov AF, Stavri G, et al. Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. J Heart Lung Transplant 2012;31:274-81.
31. Boffini M, Ricci D, Barbero C, et al. Ex vivo lung perfusion increases the pool of lung grafts: analysis of its potential and real impact on a lungtransplant program. Transplant Proc 2013;45:2624-6.
32. Andreasson A, Karamanou DM, Perry JD, et al. The effect of ex vivo lung perfusion on microbial load in human donor lungs. J Heart Lung Transplant 2014. [Epub ahead of print].
33. Sanchez PG, Davis RD, D'Ovidio F, et al. Normothermic ex vivo. lung perfusion as an assessment of marginal donor lungs - the NOVEL lung trial. J Heart Lung Transplant 2013;32:S16-7.
34. Sanchez PG, Davis RD, D'Ovidio F, et al. The NOVEL Lung Trial One-Year Outcomes. J Heart Lung Transplant 2014;33:S71-S2.
35. Machuca TN, Cypel M, Keshavjee S. Advances in lung preservation. Surg Clin North Am 2013;93:1373-94.
36. Wallinder A, Ricksten SE, Silverborn M, et al. Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: a case-control study. Eur J Cardiothorac Surg 2014;45:40-4; discussion 44-5.
37. Henriksen IS, Møller-Sørensen H, Møller CH, et al. First Danish experience with ex vivo lung perfusion of donor lungs before transplantation. Dan Med J 2014;61:A4809.
38. Warnecke G, Moradiellos J, Tudorache I, et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lungbefore bilateral transplantation: a pilot study of 12 patients. Lancet 2012;380:1851-8.
39. Israni AK, Zaun D, Rosendale JD, et al. OPTN/SRTR 2012 Annual Data Report: deceased organ donation. Am J Transplant 2014;14 Suppl 1:167-83.
40. Sanchez PG, Bittle GJ, Williams K, et al. Ex vivo lung

evaluation of prearrest heparinization in donation after cardiac death.Ann Surg 2013;257:534-41.
41. Nakajima D, Chen F, Yamada T, et al. Reconditioning of lungs donated after circulatory death with normothermic ex vivo lung perfusion. J Heart Lung Transplant 2012;31:187-93.
42. Mulloy DP, Stone ML, Crosby IK, et al. Ex vivo rehabilitation of non-heart-beating donor lungs in preclinical porcine model: delayed perfusion results insuperior lung function. J Thorac Cardiovasc Surg 2012;144:1208-15.
43. Gomez-de-Antonio D, Campo-Cañaveral JL, Crowley S, et al. Clinical lung transplantation from uncontrolled non-heart-beating donors revisited. J Heart Lung Transplant 2012;31:349-53.
44. Moradiellos FJ, Naranjo JM, Córdoba M, et al. Clinical Lung Transplantation after Ex Vivo Evaluation of Uncontrolled Non Heart-Beating Donors Lungs: Initial Experience. J Heart Lung Transplant 2011;30:S38.
45. Egan T, Blackwell J, Forrest L, et al. Evaluation of Human Lungs From Category 1 Non-Heart-Beating Donors (NHBDs) With Ex-Vivo Lung Perfusion (EVLP) in the U.S. Chest 2014;145:635A.

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Surgical Technique

The surgical technique of bilateral sequential lung transplantation

J. W. Awori Hayanga[1], Jonathan D'Cunha[2]

[1]Spectrum Health, Richards DeVos Heart & Lung Transplantation Program, Grand Rapids, MI, USA; [2]Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Correspondence to: Jonathan D'Cunha, MD, PhD. Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, UPMC Presbyterian, Suite C-900, 200 Lothrop St., Pittsburgh, PA 15213, USA. Email: dcunhaj@upmc.edu.

Abstract: Since the first successful lung transplant performed three decades ago, the technique of lung transplantation has evolved with acceptable short- and long-term outcomes such that it has become the standard for those with end stage pulmonary disease. Herein, we describe our current favored approach and discuss some of the current areas in need of further investigation as they relate to the technical aspects of the operation.

Keywords: Lung transplantation; surgical technique; end-stage lung disease; bilateral sequential lung transplantation; single lung transplantation

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Introduction

Lung transplantation is the most effective treatment modality for end-stage pulmonary disease (1-4). The number of procedures performed continues to increase every year with an estimated 3,000 transplants being performed annually (1). The majority of transplants performed today are bilateral sequential procedures (3). This is supported by evidence within the literature that has identified a long-term survival benefit from bilateral as opposed to single lung transplantation (5,6). Operative techniques and critical care, however, continue to evolve and 1- and 5-year outcomes continue to improve (5,7).

Operative approach

The decision as to whether to use extracorporeal support during bilateral lung transplantation varies with institutional experience and with patient selection. The bulk of the decision-making should be made preoperatively and can be modified based on intraoperative hemodynamic stability. Recipients are prepared for the operating room (OR) well in advance by completing their routine studies. I personally ensure that all recipient studies are confirmed using a standard checklist for our program that includes the detailed review of all pre-operative studies. We also have a pre-operative safety checklist in addition to our institutional OR standards that ensures blood type and serology acknowledgement prior to entering the OR. This is specific to our organ transplant program and is a "hard stop" in the OR flow if the documentation is not completed correctly.

Following appropriate donor selection and communication with the procurement team at the donor site, it is paramount to engage in constructive dialogue with the anesthesiology, perfusion, and OR teams so that intraoperative needs are anticipated ahead of time. This involves a discussion regarding selection of antimicrobial prophylaxis, preoperative inhaled pulmonary vasodilators (such as nitric oxide), the likelihood of requiring cardiopulmonary support, immunosuppression induction, intravascular access, and the availability of blood products. Additionally, any patient or donor-specific nuances are reviewed.

Prior to intubation, two intravenous lines and a radial arterial line are placed. The patient is intubated with a double lumen endotracheal tube that is positioned using fiberoptic bronchoscopy. The time of induction can be very destabilizing and I make it a point to be in the room ready to intervene in case of cardiopulmonary instability. A left femoral arterial line is placed. Venous access is

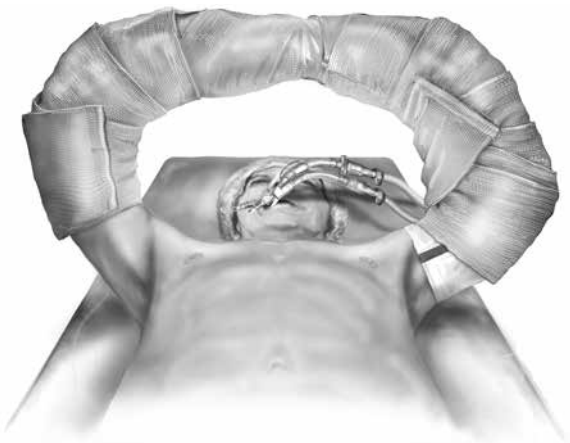

Figure 1 Patient positioning for bilateral sequential lung transplantation.

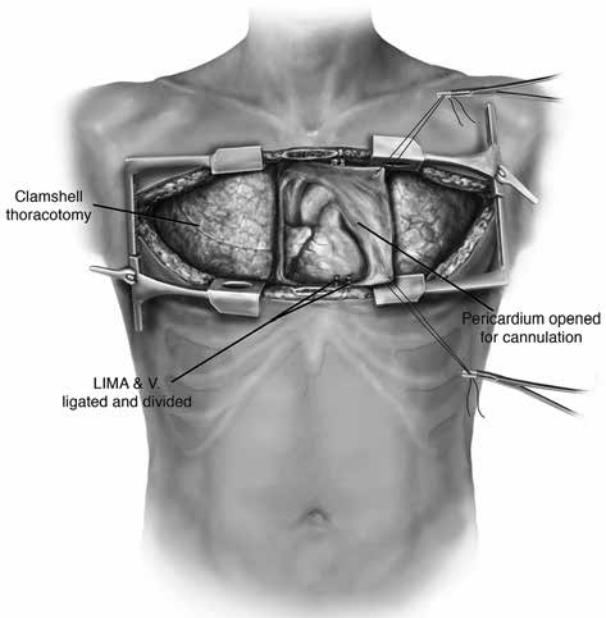

Figure 2 The approach for bilateral thoracosternotomy.

established in the right neck and left groin. If the patient is high risk or the donor lungs of marginal quality, it is prudent for the team to place the right venous neck line in the left neck in the event that post-operative extracorporeal membrane oxygenation (ECMO) may be required (the right neck would be used for a cannula during veno-venous ECMO). Placement of a pulmonary artery (PA) catheter is performed. A transesophageal echo (TEE) probe is placed in the esophagus and routine evaluation performed.

The patient is positioned supine with arms abducted, supported and padded above the head to expose both the chest and the axillary regions (*Figure 1*). The entire neck, chest, abdomen, and bilateral groins are prepped in the sterile field to allow for access to the femoral vessels in the event of the need for rapid extracorporeal support. The traditional incision used for bilateral lung transplantation is the clamshell incision, but the procedure may also be performed using separate bilateral sternal sparing anterior thoracotomies. I prefer the bilateral thoracosternotomy because of the ability to intervene with central cannulation rapidly if there is any hemodynamic compromise during the operation (*Figure 2*). This sternal-sparing anterior thoracotomy incision is a nice approach for single lung transplantation as you can easily place the patient on ECMO/CPB via the groin. Early in my practice I performed single lung transplants through posterolateral thoracotomies, but subsequently have switched to the anterior approach because of the ease of cannulation access when the patient is positioned supine.

Each of the commonly used incisions is performed by convention in the fourth (idiopathic pulmonary fibrosis) or fifth (emphysema, cystic fibrosis) intercostal space. When a clamshell incision or bilateral thoracosternotomy is performed, special care must be taken to ligate the internal mammary arteries as they can be an inconvenient source of bleeding postoperatively. Once the chest is entered, the internal thoracotomy is completed posteriorly sparing the latissimus dorsi and serratus anterior muscles. Chest retractors are placed. The mediastinal pleura is divided superiorly to the level of the mammary vein and inferiorly to the level of the pericardium.

The choice of which side should be transplanted first may be determined preoperatively by split function testing in which the worse side is transplanted first. There may, however, be other donor and recipient characteristics that dictate this decision. The lungs and chest cavity are inspected for pathologic findings. A figure-of-eight traction suture (0-silk) is placed on the dome of the diaphragm and brought out infero-medially on the external to the body. This is secured with a small clamp. The pericardium may be opened at this point or later in the case in preparation for central cannulation, to aid with hilar dissection, or to allow for intentional cardiac shifting for optimizing hemodynamics (especially for left sided anastomoses). Adhesions encountered within the chest are liberated with electrocautery. The inferior pulmonary ligament is released. The hilar dissection is then carried out and the phrenic nerve is left uninjured. Pneumonectomy is performed in a

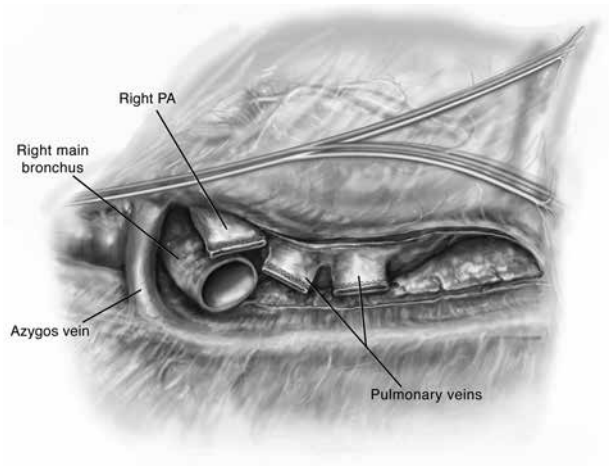

Figure 3 The view of the right hilum following recipient pneumonectomy (right side is shown).

standard fashion beginning with the division of the inferior pulmonary ligament, the sequential encircling of the PA and pulmonary veins (PV) followed by multiple firings of an endo GIA stapler staying as peripheral as possible. Before stapling the PA, it is snared down using a tourniquet for 5 to 10 minutes to assess hemodynamic stability. In the event of escalating PA pressure, the decision to use cardiopulmonary support should be made. Regardless of the circumstance, I give a small dose of Heparin (100 U/kg) systemically and keep the activated clotting times (ACTs) 160-200 once the PA is clamped. If ECMO is used then I run the ACTs 180-250. If CPB is used, the ACTs are that for standard CPB. Generally, for CPB, my preference is for central cannulation that includes an aortic cannula and a two-stage venous cannula. Of course, cannulae size and other variables are adjusted to the patient characteristics and potential need for additional cardiothoracic procedures (patent foramen ovale closure, coronary artery bypass, etc.).

For the pneumonectomy, the pulmonary vessels are divided first followed by the bronchus. On the right side the bronchus is divided immediately proximal to the takeoff of the right upper lobe. On the left side, I divide the bronchus immediately proximal to the secondary carina. During the division of the bronchus, the fraction of inspired oxygen (FiO_2) should be decreased to less than 30% and suction applied to the ipsilateral side through the double lumen ET tube so as to minimize the entrainment of high flow oxygen that could result in sparking a fire due to the simultaneous use of electrocautery. We also flood the field with CO_2. Once the pneumonectomy has been performed, the recipient lung is cultured and then sent for permanent fixation, sectioning, and pathological examination.

The hilum is then prepared by circumferentially opening the pericardium (*Figure 3*). This affords mobilization of the PVs and PA to admit clamps. The bronchus is prepared centrally and cut with an angled scalpel at the desired length. On the right side I prefer to cut at 2 rings from the carina. During this preparation the mediastinal lymph nodes are liberated such that a safe anastomosis may be performed. Bronchial arteries are ligated with cautery and clips to prevent significant bleeding. Denudation of the recipient bronchus should be avoided to prevent ischemic complications (8-10). Any secretions within the bronchus are suctioned liberally and the double lumen endotracheal tube is adjusted appropriately. The pleural space and bronchus are irrigated liberally with antibiotic-containing solution. The amount and content of irrigation is typically recipient and center-dependent.

Back table preparation is performed to ready the donor lungs for implantation. With the graft on ice, the bronchus, PVs, and PA are prepared. The donor bronchus is cultured. Extra tissue from the procurement is removed sharply or with electrocautery. The donor bronchus is trimmed to within approximately 1-2 rings from the lobar takeoffs. We use crushed ice to keep the recipient thoracic cavity cool during the implantation with a "phrenic pad" placed *in situ* to protect graft from warming and from direct contact with the body wall. The implantation is then conducted sequentially beginning with the most posterior anatomical structure, the bronchial anastomosis (*Figure 4*). The bronchial anastomosis is completed using a running 3-0 polypropylene suture which begins with the membranous portion of the airway and ends anteriorly on the cartilaginous portion. The anastomosis is performed in an end-to-end fashion taking great care to achieve membranous-to-membranous and cartilaginous-to-cartilaginous apposition. My preference is to reinforce the suture line at 10 and 2 o'clock with two additional 3-0 polypropylene stitches thereby locking the continuous suture line in place. The anastomosis is immediately inspected using bronchoscopy. In our experience, we routinely tack an edge of intervening donor pericardium to separate the bronchus from the PA.

The PA anastomosis is fashioned next following the infusion of 500-700 mL of pulmoplegia into the PA using a handheld antegrade cannula. This flows from retrograde exiting through the PV and is recirculated using "cell saver". A Satinsky clamp is placed proximally on the PA

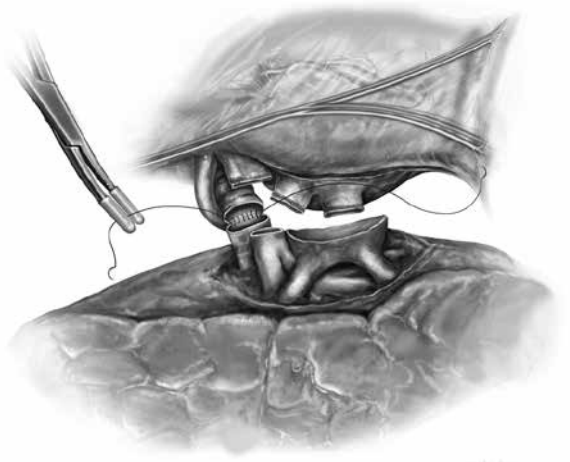

Figure 4 The bronchial anastomosis.

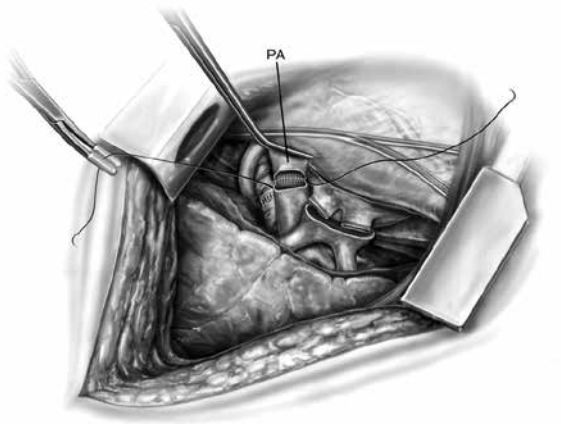

Figure 5 The pulmonary artery (PA) anastomosis.

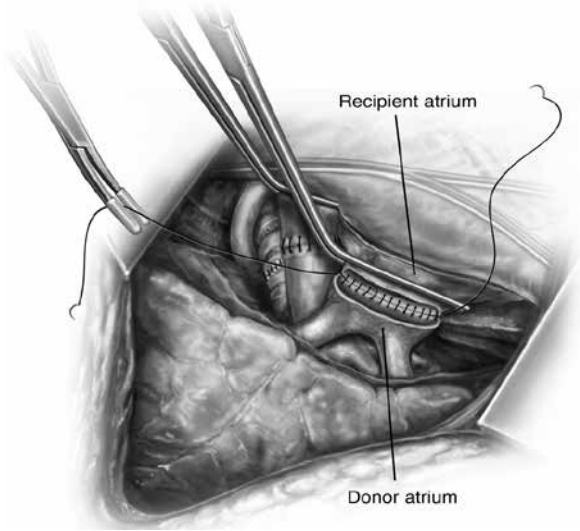

Figure 6 The left atrial anastomosis.

and the staple line is removed. The donor PA is trimmed to an appropriate length. Care must be taken to not leave the donor PA too long or too short such that problems with kinking or tearing are avoided respectively. The PAs are aligned and anastomosed using a continuous 5-0 polypropylene suture (*Figure 5*). At the completion of the suture line, they are clamped and not secured until later.

The left atrial anastomosis is next and this is aided by circumferential mobilization of the left atrium within the pericardium. A large Satinsky clamp is placed on the body of the left atrium. The staple lines of the superior PV and the inferior PV are excised and connected creating a recipient cuff for anastomosis. An endothelial to endothelial, end-to-end anastomosis is then performed using a running 4-0 polypropylene suture (*Figure 6*). Attention is taken to include the intima and exclude the muscle from the suture line. As the anastomosis nears completion, the anesthesiologist should administer 250-500 mg IV methylprednisolone.

We do not immediately knot down the anastomoses and instead allow for flushing and de-airing using 500-700 mL of "hotshot pulmoplegia" administered using a handheld cardioplegia cannula in antegrade fashion, thereby reperfusing the allograft. The Satinsky clamp on the PV is then partially opened to deair and the PV knot is tied. The PA is then unclamped over the course of 5-15 minutes and the suture line is secured. This affords controlled low pressure perfusion of the lung. Ventilation with minimal FiO_2 (preferably less than 30%) is initiated by hand and then by mechanical ventilation. A gentle Valsalva may be performed to overcome atelectatic de-recruitment and allow for efficient expansion of the lung. At this point the chest is irrigated and the bronchus tested for leak under saline immersion to a pressure of 25-35 cm H_2O. Once satisfied with this, positive end-expiratory pressure (PEEP) is set at 8-10 cm H_2O and the patient is ventilated under pressure control or with tidal volumes approximately 5-7 mL/kg donor weight. Intraoperative TEE is utilized to evaluate for de-airing and gradient measurement across the PVs and PA. The suture lines are inspected for hemostasis and once satisfied with this, the patient is allowed to recover during this time for 10-15 minutes before the opposite side is addressed in an exact analogous fashion.

By convention, we place three chest tubes in each pleural cavity. A large bore chest tube is positioned anteriorly in the chest. A 24F Blake drain is placed along the diaphragm and posteriorly towards the apex in the chest. A third large bore right angled chest tube is placed posterolaterally.

This is the same for each chest. If the pericardium was opened as I do in the vast majority of transplants, a 24F Blake drain is placed in the pericardium. The bilateral thoracotomy incision is closed using interrupted #5 Poly (ethylene, terephthalate) suture in a figure-of-eight fashion. The sternum approximated using three number 6 sternal wires. The pectoral fascial layer, the subcutaneous layer, the subdermal layer, and the skin are reapproximated with absorbable suture. Recently, we have been much more liberal with staples for skin closure. If the lungs are oversized, there is significant PGD, or hemodynamic instability, we leave the chest open according to that method previously described (11).

The double lumen endotracheal tube is exchanged for a single lumen endotracheal tube and bronchoscopy is performed for pulmonary toilet immediately post procedure. During this time a nasoenteric feeding tube is also placed with the added benefit of performing this under endoscopic control of the airway to avoid the inadvertent placement of the feeding tube within the airway. We typically use conservative FiO_2 concentration of 40% in the immediate postoperative phase to avoid theoretical risk of free radical-induced oxygen toxicity and PEEP of 10. Adjuncts such as Nitric oxide and epoprostenol should be weaned off expeditiously in the first 12-24 hours postoperatively to allow for prompt extubation.

Areas of debate related to technique

There have been a number of unsuccessful efforts in the past at reaching a consensus regarding various technical aspects of lung transplantation. Attempts, for example, made to reduce the incidence of the risk of airway complications have resulted in the varying popularity of a number of techniques (12-14). This has included telescoping of the bronchial anastomosis, the use of vascularized pedicle flaps, and even bronchial artery revascularization (15-21). We believe that the increased technical detail and variation in experience with these various steps has not allowed for any consensus beyond what we have described in this report. We also recognize that the intraoperative use of pulmoplegia before and after the fashioning of the pulmonary anastomoses is not a universally accepted practice. I have performed transplants both ways and observed no distinct differences. Thus, the use of pulmoplegia is an area deserving of further investigation.

The debate between the use of interrupted versus continuous suture techniques for the bronchial anastomosis continues to garner supporters on either side of the argument. FitzSullivan and colleagues described the use of continuous suture on the membranous bronchus and interrupted figure-of-eight suturing of the cartilaginous bronchus (14). Weder and colleagues on the other hand, prescribe the use of interrupted suture circumferentially around the entire anastomoses (22). Both groups, as is typically the case, reported satisfactory results and a reduction in airway complications. I perform a modified version of the continuous anastomosis placing two additional interrupted sutures for two reasons. One, it allows me to rest more easily knowing that there are additional sutures and the continuous suture line does not depend on one single running polypropylene suture. Two, if the anastomosis falls apart, I can blame myself such that the trainee that typically sews the continuous suture line is alleviated of the responsibility for this complication.

There has also been a growing trend in the use of lobar lung transplantation which has been fueled by the paucity of donors and the increasing need to match larger donors with smaller recipients. This has resulted in an increased consideration for lobar lung transplantation and outcomes have been acceptable where the simpler procedure of graft reduction was not considered a durable option (23-25).

Conclusions

The technique of bilateral sequential lung transplantation has evolved over the years to make it relatively safe operation when combined with careful pre-operative candidate selection, careful donor selection, and advances in critical care. The improvement in early patient survival has been achieved by a reduction in the overall rate of PGD to 5-15%. Post-operatively, severe PGD as marked by hypoxia, pulmonary edema, elevated PA pressures, and poor compliance needs to be recognized early and intervened on. We advocate for early institution of veno-venous (V-V) ECMO when recipients are deteriorating and require FiO_2 >70% to better manage the patient and avoid further injury from barotrauma.

The hallmark of post-operative care is a team approach which should mirror that of the team approach to patient selection. This includes involving anesthesia with relationship to pain control as the placement of paravertebral catheters may be of substantial benefit in recovery. There is no doubt that a dedicated intensivist with experience in cardiothoracic surgery is critical to managing fluids, hemodynamics, and optimizing the outcome of

end organ perfusion. We have also instituted a clinical pathway to aim towards early extubation and recovery that involves multidisciplinary input from pulmonary medicine, pharmacists, transplant infectious disease, cardiopulmonary rehab, etc. This has led to tremendous progress in lung transplantation over the past several years with 1-year and 5-year survival rates comparable to those of other solid organs. Although organ supply is remains limited, the current era of *ex vivo* lung perfusion (EVLP) holds great promise for increasing the number of organs available, (re)assessment of graft performance, and potentially repair/reconditioning of donor organs (26,27). This is an exciting time for lung transplantation and investigations into some of the newer areas of lung transplantation, such as EVLP, should afford improved understanding of the nuances of the surgical technique and ultimately translate into improved early and late outcomes for patients with end-stage lung disease.

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References

1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report--2010. J Heart Lung Transplant 2010;29:1104-18.
2. DeMeo DL, Ginns LC. Lung transplantation at the turn of the century. Annu Rev Med 2001;52:185-201.
3. Cai J, Mao Q, Ozawa M, et al. Lung transplantation in the United States: 1990-2005. Clin Transpl 2005:29-35.
4. Arcasoy SM, Kotloff RM. Lung transplantation. N Engl J Med 1999;340:1081-91.
5. Yusen RD. Survival and quality of life of patients undergoing lung transplant. Clin Chest Med 2011;32:253-64.
6. Weiss ES, Allen JG, Merlo CA, et al. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. Ann Thorac Surg 2009;88:1616-25; discussion 1625-6.
7. Yusen RD, Shearon TH, Qian Y, et al .Lung transplantation in the United States, 1999-2008. Am J Transplant 2010;10:1047-68.
8. Puri V, Patterson GA. Adult lung transplantation: technical considerations. Semin Thorac Cardiovasc Surg 2008;20:152-64.
9. Boasquevisque CH, Yildirim E, Waddel TK, et al. Surgical techniques: lung transplant and lung volume reduction. Proc Am Thorac Soc 2009;6:66-78.
10. Aigner C, Klepetko W. Bilateral lung transplantation. Operative Tech Thorac Cardiovasc Surg 2012;17:181-93.
11. D'Cunha J, Rueth NM, Belew B, et al. The effectiveness of the "open chest" for the unstable patient after bilateral sequential lung transplantation. J Heart Lung Transplant 2010;29:894-7.
12. Kshettry VR, Kroshus TJ, Hertz MI, et al. Early and late airway complications after lung transplantation: incidence and management. Ann Thorac Surg 1997;63:1576-83.
13. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: ischemia, dehiscence, and stenosis. Proc Am Thorac Soc 2009;6:79-93.
14. FitzSullivan E, Gries CJ, Phelan P, et al. Reduction in airway complications after lung transplantation with novel anastomotic technique. Ann Thorac Surg 2011;92:309-15.
15. Fell SC, Mollenkopf FP, Montefusco CM, et al. Revascularization of ischemic bronchial anastomoses by an intercostal pedicle flap. J Thorac Cardiovasc Surg 1985;90:172-8.
16. Chhajed PN, Malouf MA, Tamm M, et al. Interventional bronchoscopy for the management of airway complications following lung transplantation. Chest 2001;120:1894-9.
17. Higgins R, McNeil K, Dennis C, et al. Airway stenoses after lung transplantation: management with expanding metal stents. J Heart Lung Transplant 1994;13:774-8.
18. Mizobuchi T, Sekine Y, Yasufuku K, et al. Comparison of surgical procedures for vascular and airway anastomoses that utilize a modified non-suture external cuff technique for experimental lung transplantation in rats. J Heart Lung Transplant 2004;23:889-93.
19. Nicolls MR, Zamora MR. Bronchial blood supply after lung transplantation without bronchial artery revascularization. Curr Opin Organ Transplant 2010;15:563-7.
20. Siegelman SS, Hagstrom JW, Koerner SK, et al. Restoration of bronchial artery circulation after canine lung allotransplantation. J Thorac Cardiovasc Surg 1977;73:792-5.
21. Veith FJ, Richards K. Improved technic for canine lung transplantation. Ann Surg 1970;171:553-8.
22. Weder W, Inci I, Korom S, et al. Airway complications after lung transplantation: risk factors, prevention and outcome. Eur J Cardiothorac Surg 2009;35:293-8; discussion 298.
23. Shigemura N, Bhama J, Bermudez C, et al. Lobar lung

transplantation: emerging evidence for a viable option. Semin Thorac Cardiovasc Surg 2013;25:95-6.
24. Inci I, Schuurmans MM, Kestenholz P, et al. Long-term outcomes of bilateral lobar lung transplantation. Eur J Cardiothorac Surg 2013;43:1220-5.
25. Shigemura N, D'Cunha J, Bhama JK, et al. Lobar lung transplantation: a relevant surgical option in the current era of lung allocation score. Ann Thorac Surg 2013;96:451-6.
26. Munshi L, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. Lancet Respir Med 2013;1:318-28.
27. Whitson BA, D'Cunha J. Ex vivo lung perfusion and extracorporeal life support in lung transplantation. Semin Thorac Cardiovasc Surg 2011;23:176-7.

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Review Article

Bridge to lung transplantation and rescue post-transplant: the expanding role of extracorporeal membrane oxygenation

Brian C. Gulack, Sameer A. Hirji, Matthew G. Hartwig

Department of Surgery, Duke University Medical Center, Durham, NC, USA

Correspondence to: Matthew G. Hartwig, MD. Department of Surgery, Division of Thoracic Surgery, Duke University Medical Center, Box# 3863, Durham, NC 27710, USA. Email: matthew.hartwig@duke.edu.

Abstract: Over the last several decades, the growth of lung transplantation has been hindered by a much higher demand for donor lungs than can be supplied, leading to considerable waiting time and mortality among patients waiting for transplant. This has led to the search for an alternative bridging strategy in patients with end-stage lung disease. The use of extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation as well as a rescue strategy post-transplant for primary graft dysfunction (PGD) has been studied previously, however due to initially poor outcomes, its use was not heavily instituted. In recent years, with significant improvement in technologies, several single and multi-center studies have shown promising outcomes related to the use of ECMO as a bridging strategy as well as a therapy for patients suffering from PGD post-transplant. These results have challenged our current notion on ECMO use and hence forced us to reexamine the utility, efficacy and safety of ECMO in conjunction with lung transplantation. Through this review, we will address the various aspects related to ECMO use as a bridge to lung transplantation as well as a rescue post-transplant in the treatment of PGD. We will emphasize newer technologies related to ECMO use, examine recent observational studies and randomized trials of ECMO use before and after lung transplantation, and reflect upon our own institutional experience with the use of ECMO in these difficult clinical situations.

Keywords: Lung transplantation; extracorporeal membrane oxygenation (ECMO); primary graft dysfunction (PGD)

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Introduction

The prevalence of lung transplantation has increased significantly over the last few decades, especially in the treatment of end stage lung diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and cystic fibrosis (CF) (1). In 2012, over 3,640 lung transplants were recorded in the registry of the International Society for Heart and Lung Transplantation, up from 3,395 the year before (1). Early survival following lung transplantation has improved over the years with 1-year survival approaching 79% (1). Unfortunately, the long-term success of lung transplantation has only seen a modicum of improvement, with median survival for the most recent era averaging 6.1 years (1).

Due to its modest successes and changing demographics, waiting time for lung transplantation continues to be an issue as the need for donor organs far exceeds their availability (2). While the implementation in the United States of the lung allocation score (LAS) in 2005 has helped to prioritize patients in the most urgent need for transplantation, roughly 500 patients continue to die while awaiting a lung transplant every year (3-5). The resulting estimates of mortality for patients on the waitlist is concerning, and has raised considerable interest in looking for alternative bridging strategies for patients with end-stage lung disease awaiting transplantation (2).

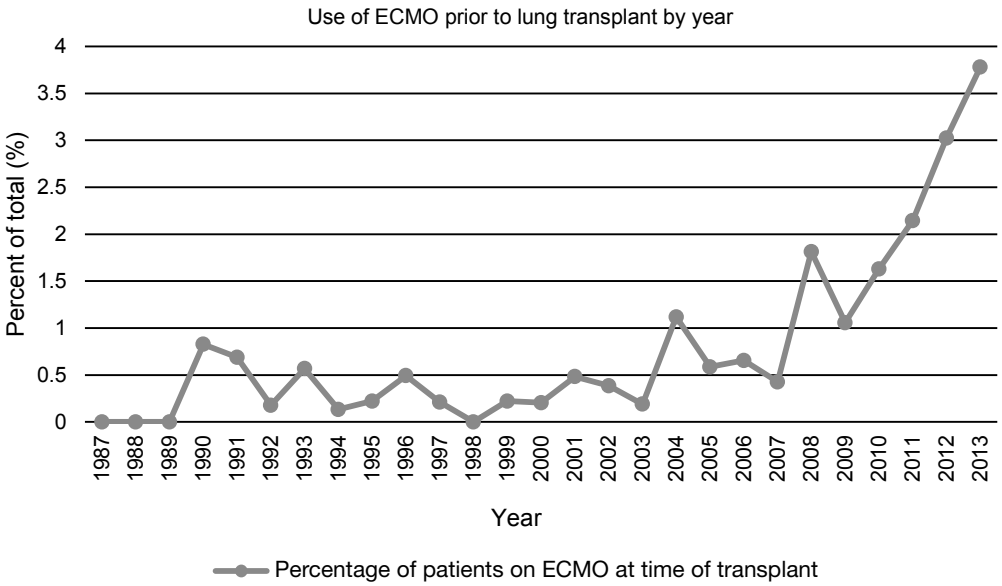

Figure 1 Percentage of patients on ECMO at time of transplant by year. Data obtained from the United Network for Organ Sharing (UNOS) database 1987-2013. Only patients with no previous transplant were included. ECMO, extracorporeal membrane oxygenation.

Utility of ECMO

Extracorporeal membrane oxygenation (ECMO) is a complex technique that allows for respiratory and/or cardiac support in critically ill patients (6). There are many indications for the implementation of ECMO, including adult respiratory distress syndrome (ARDS), inability to wean from cardiopulmonary bypass, and cardiogenic shock, among others (7). It can be used both in a veno-venous (VV) circuit for pure pulmonary support as well as a veno-arterial (VA) circuit for concomitant cardiac support (8-10). Cannulation strategies and implantation techniques vary tremendously based upon the local environment, resources and patient needs (6-8). Because of the technical expertise required and considerable financial costs, its use has been limited to patients with a high risk of mortality and whose underlying disease process is either reversible or as a short-term "bridge" to more definitive therapy (11).

Over the last several years, the use of ECMO as a bridge to lung transplantation has gained significant attention in the management of patients with severe end-stage lung disease (9,12). Historically, ECMO use in this setting has been associated with poor outcomes which led many to condemn the practice (13,14). However, in recent years, technical advances have resulted in the extended use of various extracorporeal life support (ECLS) devices, such as ECMO, in the management of patients presenting with acute respiratory failure with significant improvement in outcomes (15). Furthermore, the implementation of the LAS has led to decreasing waiting times for lung transplantation (16). Combined, this has also led to a reinvigoration in the use of ECMO as a bridge to lung transplantation. In a study of more than 9,000 patients from the UNOS database from 2005 to 2011, roughly 1% of pulmonary patients were bridged to transplant with ECMO support (5). These numbers have continued to grow since then as an increasing number of single-center studies have demonstrated the utility and successful outcomes associated with ECMO as a bridging strategy to lung transplantation (*Figure 1*) (17-23).

Historical challenges

There has been significant variability in the use of ECMO as a means of bridging patients to lung transplantation over its short history (*Figure 2*). Hill *et al.* first reported the use of ECMO as a treatment modality for the management of cardiopulmonary failure in 1972 (24). Shortly thereafter in 1975, ECMO was described as a means of bridging a patient to lung transplantation, however further use was impeded by poor initial outcomes (13,14,25). Unacceptable post-transplant survival following pre-operative ECMO was likely

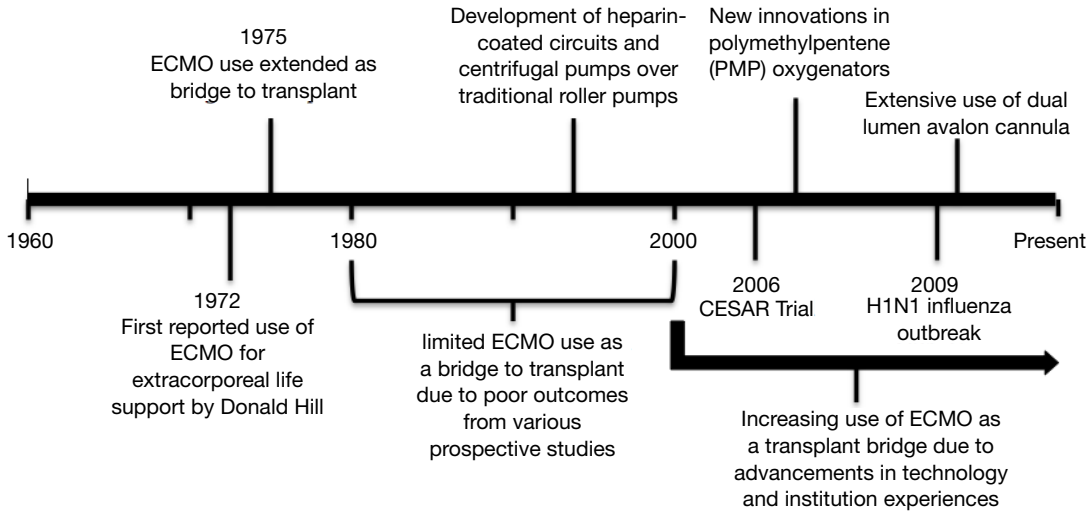

Figure 2 Historical points of interest in the use of ECMO as a bridge to lung transplantation. ECMO, extracorporeal membrane oxygenation.

related to both the severity of the patient's illness and the technological inadequacies of early ECMO systems (17). Furthermore, it was traditionally regarded that ECMO use pre-transplant was associated with impaired bronchial anastomotic healing that contributed to the morbidity and mortality in lung transplant recipients (25). In addition, the results of a randomized, prospective study in 1979 demonstrating no survival benefit from ECMO in a non-lung transplant cohort of patients with acute respiratory failure further contributed to this declining use (18).

For the next two decades, the use of ECMO as a bridge to lung transplant was only sporadically used and limited to a few centers with mixed outcomes. However, significant improvements in ECMO-related technologies were made during this time period and data accrued slowly that challenged earlier preconceptions about the utility of ECMO (19,20). For example, during the 2009 H1N1 influenza outbreak, ECMO gained special attention by successfully managing a significant proportion of patients with severe acute respiratory failure (19). Furthermore, the *Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR)* trial was conducted in the United Kingdom, and demonstrated a significant survival benefit of ECMO compared to conventional management for patients with severe ARDS (20).

ECMO as a rescue strategy post-transplant

Background

In lung transplantation a renewal of interest in ECMO was first seen for severe primary graft dysfunction (PGD) following lung transplantation and this remains the most common indication for its use after transplant (21,22). PGD is a syndrome consisting of lung injury during the first 72 hours following lung transplant defined as a decreased PaO_2/FiO_2 ratio and the presence of diffuse infiltrates on chest X-ray (23,26). As institutional experience with ECMO accrued, several isolated studies and case reports explored the use of ECMO as a rescue strategy in the treatment of PGD post lung transplantation, and as a bridge to redo lung transplant in select patients with intermittent successes (27,28). About 5% of lung transplant procedures require ECMO support for PGD or early complications (21). Many interventions have been studied to try and ameliorate the effects of PGD after transplant, including experimentation with inhaled nitric oxide and prostaglandins (29,30). However, none of these have been successful in significantly altering the rates of clinically important Grade 3 PGD, which hovers at about 17% according to results of the Lung Transplant Outcomes Group (26). According to this multi-institutional study, grade 3 PGD was associated with a 23% absolute increase in the risk of death within one year of transplant, indicating it's continued overall impact on transplant survival (26).

Indications

An important question remains regarding when to employ ECMO after transplantation. Enhanced safety combined with increased experience has led to earlier

deployment of ECMO circuits to support patients after lung transplantation (31). The goal should be to avoid or minimize the detrimental effects of ventilator support for PGD secondary to elevated airway pressures or high inspired oxygen concentrations. Firm guidelines vary from center to center, but we recommend initiating ECMO support when ventilatory requirements reach a peak inspiratory pressure of 35 cm H_2O or F_iO_2 surpasses 60% in order to minimize lung injury from aggressive mechanical ventilation and oxidative stress. When necessary, the delayed initiation of ECMO after transplantation greater than 48 hours has been associated with worse outcomes, and this is consistent with our own experience that favors prompt initiation of ECMO (32).

Outcomes

Our group and others have reported on utilizing ECMO to support the recipients who suffer from severe PGD. Survival in this group of patients was surprisingly good when supported with VV ECMO, especially considering the lethality of severe PGD (22). The mean reported ECMO duration post-transplant is varied, but most studies have reported between 2 to 8 days (21,28,33). One study demonstrated successful use of ECMO for 3 weeks prior to a redo lung transplantation, however others have demonstrated that prolonged ECMO duration post-transplant is associated with high mortality (28,34). Nonetheless, it provides a means of treatment in patients who suffer from PGD post-operatively who would otherwise succumb quickly. We have reported a 96% success rate in weaning recipients from VV ECMO following transplant, with a 30-day survival of 82% and 1-year survival of 64% (22). Some centers report success with both VA and VV ECMO for these patients. However, our experience has been that VV ECMO should be preferred due to a decrease in complications and greater survival when compared to patients supported with VA ECMO (21).

ECMO as a bridge to transplant

Background

In the last several years, there has also been a continued push at individual centers to reexamine lung transplantation in patients on ECMO. Numerous reasons are cited for this including a benefit in weaning patients off of mechanical ventilation (which is also associated with increased post-operative mortality) as well as allowing patients with acute respiratory failure to be transported to centers with transplant services from those without (35-37). Others use recent advancements in technology as an argument for reexamining this issue. For instance Jackson *et al.* list three major recent advancements in ECMO: the development of the polymethylpentene (PMP) oxygenator, the use of heparin coated circuits, and the use of centrifugal pumps over traditional roller pumps (25). We would add portability and the dual-lumen cannula to this list and emphasize that together these advances have led to the ability to minimize anticoagulation needs and likely result in much less hemolysis and activation of blood components traveling through the circuit.

Indications

Although multiple centers have published with regards to their successes transplanting patients following the use of VV ECMO, there are no universally accepted indications for this practice (10,27,38). Careful patient selection for lung transplantation after ECMO is imperative to maximize outcomes and ensure appropriate resource allocation of scarce donor lungs. Current recommendations are based on institutional experience. Much of the earliest use of ECMO as a bridge to lung transplantation was for patients with PGD requiring retransplantation, and therefore this was seen as an early indication (39). Since that time however, improving outcomes have led to the use of ECMO bridging in patients without prior transplantation (13,39). Most studies recommend the use of this practice primarily in younger patients who suffer an acute decompensation in a chronic pulmonary process, not for acute respiratory distress syndrome (9,39). Furthermore, these patients should have had reasonable functional status prior to their acute episode (35,39). However, there has been anecdotal success in bridging previously healthy young patients to transplant when they suffer irreversible lung injury acutely.

Contraindications

Current contraindications for lung transplantation following ECMO are also based on institutional experience (*Table 1*). For instance, Lafarge *et al.* recommended that renal failure be considered a contraindication for transplantation following ECMO due to the intraoperative death of a patient who had pre-transplant anuric renal failure (10). Toyoda *et al.* recommended this be expanded to

Table 1 Contraindications (both absolute and relative) to bridging to lung transplant with ECMO (9,10,37,39,40)

Absolute contraindication
Untreated infection
Organ failure (other than pulmonary)
Recent malignancy
Active substance abuse
Poor social support system
History of nonadherence
Relative contraindication
Advancing age
Small institutional experience
Poor pre-ECMO functional status
Severe obesity (BMI >30)

ECMO, extracorporeal membrane oxygenation.

Table 2 Overview of recent single and multi-institution studies reviewing outcomes following lung transplantation after ECMO

Study	Number of patients	1-year survival (%)
Toyoda *et al.* [2013] (9)	24	74
Hoopes *et al.* [2013] (12)	31	93
Anile *et al.* [2013] (44)	7	85.7
Nosotti *et al.* [2013] (43)	11	85.7
Lafarge *et al.* [2013] (10)	30	66.5
Bittner *et al.* [2012] (27)	27	33
Gottlieb *et al.* [2012] (42)	60	57
Lang *et al.* [2012] (38)	34	60
Hämmäinen *et al.* [2011] (13)	13	92

ECMO, extracorporeal membrane oxygenation.

any organ failure including liver failure (9). Other studies including those by Bermudez *et al.* and Mason *et al.* discuss how pre-transplant ECMO populations tend to be younger, likely demonstrating inherent selection biases (9,37,39). Further research is necessary to determine if increased age is an absolute or relative contraindication. Multiple studies have also documented that their institutional outcomes have improved over time, likely secondary to a mixture of newer technology/protocols as well as extensive experience (39). As lower-volume centers are often limited in experience, ECMO use as a bridge to transplant should likely be limited at these centers until standardized best-practice protocols have been developed to optimize outcomes (9). Lastly, traditional contraindications to lung transplantation including uncontrolled or untreated infection, recent malignancy, significant coronary artery disease, and active substance abuse among others continue to be contraindications to the use of ECMO-bridged transplantation (40).

Outcomes

Although several trials have evaluated the outcomes of ECMO in severe respiratory failure, very few have examined in isolation, the utility and role of ECMO as a bridge to lung transplantation. Current literature is limited to several single center retrospective studies advocating for the use of ECMO as an alternative "salvage" therapy in patients with end-stage lung disease (9,10,12,13,27,35,36,38,41-44). Most of these analyses were composed of a mixture of ambulatory/extubated patients and sedated/intubated patients. A summary of these studies can be found in *Table 2*. One year survivals ranged from 33-93%, many of which are better than that reported previously (9,10,12,13,17,27,37,38,43,44). Moreover, diagnoses in these groups varied, but overall CF and idiopathic pulmonary fibrosis (IPF) had a higher prevalence while COPD had a lower prevalence than that of the general lung transplant population (1,9,10,12,35,36,38,41,42). As an indication of the changing times, there has been over a 200% increase in lung transplantation in patients on ECMO between 2009-2013 (*Figure 1*).

The discrepancy noted in survival outcomes among the above referenced studies is unclear; however, we speculate that this may be attributable to the nature of ECMO used, institutional differences in cannulation strategies, disparate wait list times among centers, and the extent and severity of post-transplant complications such as PDG. Furthermore, several studies have also shown that although high acuity lung transplant patients who are bridged with ECMO have increased risk for short-term mortality compared to the average lung transplant recipient, these high-risk recipients have better overall outcomes when performed at high volume centers (5). It is likely that this success is secondary to the extensive experience and technological capabilities in managing the complexities associated with ECMO at high volume centers. It may also be secondary to shorter waiting times at these high volume centers subsequently leading to a shorter pre-transplant ECMO duration and improved survival.

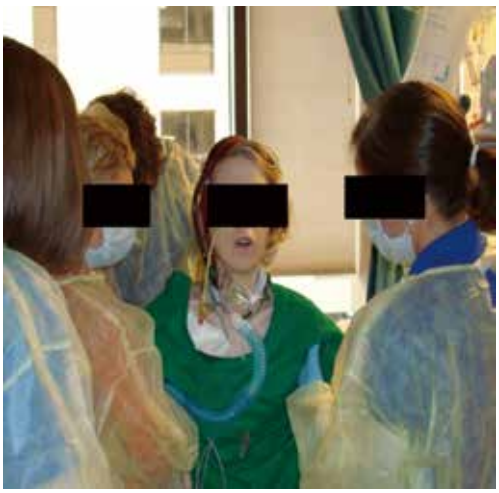

Figure 3 Demonstration of a patient ambulating on VV ECMO with a dual lumen cannula in the right internal jugular vein. VV, veno-venous; ECMO, extracorporeal membrane oxygenation.

Newer treatment modalities

With the advancement of technology and increase in institutional experience in the past few years, newer and more promising strategies of incorporating the use of ECMO as a bridge to transplant have been developed. For instance, Fuehner *et al.* examined outcomes using ECMO as a bridge to transplantation in patients who were awake and spontaneously breathing. Compared to the conventional mechanical ventilation strategy, patients who received "awake" ECMO as a bridge to transplant and made it to transplantation had significantly better survival at 6 months (80% versus 50%), and had shorter postoperative hospital stays (although not to statistical significance) (41). The authors hypothesize that the main benefit of this "awake" ECMO is the avoidance of prolonged sedation and intubation and its associated complications (41). The authors further postulate that future successes in this arena could lead to a "destination therapy" much like that seen with left ventricular assist devices (41).

Other recent advances including low-resistance gas exchange membranes, high-durability centrifugal blood pumps, heparin-coated tubing, and improved cannulation strategies have resulted in a much safer medical device compared to those in use a few years ago (45,46). Newer devices are also increasingly smaller and lightweight. The new "Cardiohelp" by Maquet Cardiopulmonary is light enough to be carried by the patient, and also can simultaneously measure patient vitals, venous oxygen concentration, and hemoglobin (47,48). Haneya *et al.* reported on its use in 22 patients with a survival rate of 68.2% (47). Further advantages of these smaller systems include easier inter-facility transport of patients, which once again can allow transport of a patient to a transplant center when indicated (48).

Our institutional experience

Taking the concept of awake ECMO one step further we recently published on our institutional experience with pre-operative ECMO in bridged patients able to perform active rehabilitation. This experience included nine patients, all of whom survived through 1-year post-transplant (17). The patients who were able to undergo active rehabilitation while awaiting lung transplantation on ECMO demonstrated shorter post-transplant ventilator duration and hospital lengths of stay. This is due to the absence of post-transplant myopathy secondary to participation in active rehab. Our rehab protocol begins with the weaning of sedation and ventilator settings. Most of the patients will require tracheostomy, which is performed early in the process or at the time of ECMO cannulation. A few patients may be extubated while on ECMO. Resistance and stretching exercises follow once awake. The patients then progress through sitting, standing, and eventually ambulation. At least two formal rehab sessions are performed each day with staffing consisting of a physical therapist, ECMO specialist, respiratory therapist and 1-2 bedside nurses. Although resource intensive, patients have demonstrated the ability to walk up to 400 meters during one session and outcomes appear to be considerably improved.

Technical aspects of ECMO

Historically, extracorporeal support required dual cannulation, such as the femoral and internal jugular veins for VV or femoral vein and artery for VA ECMO. Femoral cannulation sites may increase the risk of infection and impede patient mobility. Therefore, whether it is for bridging to transplant or support after transplant, our most commonly employed ECMO strategy now involves a VV technique utilizing a dual-lumen cannula (Avalon Maquet) in the right internal jugular vein (*Figure 3*) (49). However, many other cannulation strategies are possible for both VV as well as VA ECMO and are oftentimes dictated by patient

anatomic limitations or other factors (6,9,35). For active rehabilitation on VA ECMO, our most common approach is to sew a 6 to 8 mm vascular graft to the right axillary artery with a 21 to 23 mm venous cannula in the right internal jugular vein for drainage. Based on our experience, if at all possible we recommend a cannulation and ICU management strategy that will allow for active rehabilitation while awaiting lung transplantation on ECMO support.

Complications related to ECMO

Complications resulting from ECMO use are common, and depend on the type of ECMO technique (VA or VV) as well as the cannulation strategy used (7,9). Usual complications include bleeding, infection, and renal failure as well as less common complications including gas embolism, stroke, and limb ischemia (8,11,50,51). Bleeding is perhaps the most commonly reported complication ranging from 5-79% in the literature (11,52). Its cause is multifactorial, both secondary to iatrogenic anticoagulation necessary for ECMO as well as thrombocytopenia and fibrinolysis occurring because of contact with the ECMO circuit (11,53). Treatment is best performed through prevention, and modern circuits as described above allow users to reduce the requirement for systemic anticoagulation (11,53).

Although difficult to predict, it is pertinent to quickly identify and treat these complications to reduce associated mortality. Limb ischemia is a specific complication for which prompt diagnosis and action can improve outcomes. Occurring in 13-25% of VA ECMO patients cannulated through the femoral artery, its incidence can be reduced through use of a secondary distal catheter to increase distal limb perfusion, or through reliance on VV ECMO whenever possible to avoid arterial cannulation (54,55). Proper anticoagulation can also prevent emboli formation in the ECMO circuit. When limb ischemia is diagnosed early, prompt treatment can avoid permanent limb injury and reduce the amputation rate (54,56).

Conclusions

Lung transplantation is now considered an appropriate therapeutic option for the treatment of patients with end-stage lung disease (5). However, given the paucity of available donors, there is still significant mortality for patients on the waiting list (2). Historically, the use of extracorporeal circulatory support such as ECMO was considered to be a contraindication to lung transplantation due to poor outcomes (14). However, in recent years, this trend is evolving as more institutions look to optimize the safety and efficacy of their ECMO strategies as a means of bridging high-risk and high-acuity patients for lung transplant (44).

As larger institutional studies are performed, a clearer picture as to the outcomes of ECMO use is emerging. Some are already calling for a randomized multicenter controlled trial to help give an answer to this question (57). However, there are still many unanswered questions remaining and a randomized trial of adequate size is unlikely to ever be successfully performed. Therefore, it will be up to the lung transplant community to determine issues such as how the need for pre-transplant ECMO should weigh in to organ allocation, or what the appropriate indications and patient populations to bridge to lung transplantation should be. No doubt that as technologies continue to improve we will be obliged to revisit these questions, as well as many others periodically.

Modern experience with ECMO and reported institutional experiences on survival challenge historical assumptions about the treatment of end-stage lung disease and suggest that "bridging" to transplant with ECMO is both technically feasible and logistically viable. What is clear at this point in time is that continued advances in the technologies and further research will help determine how best to include ECMO as a bridging strategy for lung transplantation.

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References

1 Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report---2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
2 Gottlieb J. Update on lung transplantation. Ther Adv Respir Dis 2008;2:237-47.
3 Yusen RD, Shearon TH, Qian Y, et al. Lung transplantation in the United States, 1999-2008. Am J Transplant 2010;10:1047-68.
4 Egan TM, Murray S, Bustami RT, et al. Development of

the new lung allocation system in the United States. Am J Transplant 2006;6:1212-27.
5 George TJ, Beaty CA, Kilic A, et al. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. J Heart Lung Transplant 2012;31:1182-91.
6 Sidebotham D, Allen SJ, McGeorge A, et al. Venovenous extracorporeal membrane oxygenation in adults: practical aspects of circuits, cannulae, and procedures. J Cardiothorac Vasc Anesth 2012;26:893-909.
7 Allen S, Holena D, McCunn M, et al. A review of the fundamental principles and evidence base in the use of extracorporeal membrane oxygenation (ECMO) in critically ill adult patients. J Intensive Care Med 2011;26:13-26.
8 Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: part 2-technical considerations. J Cardiothorac Vasc Anesth 2010;24:164-72.
9 Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg 2013;145:1065-70; discussion 1070-1.
10 Lafarge M, Mordant P, Thabut G, et al. Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant 2013;32:905-13.
11 Lafç G, Budak AB, Yener AÜ, et al. Use of extracorporeal membrane oxygenation in adults. Heart Lung Circ 2014;23:10-23.
12 Hoopes CW, Kukreja J, Golden J, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013;145:862-7; discussion 67-8.
13 Hämmäinen P, Schersten H, Lemström K, et al. Usefulness of extracorporeal membrane oxygenation as a bridge to lung transplantation: a descriptive study. J Heart Lung Transplant 2011;30:103-7.
14 Veith FJ. Lung Transplantation. Transplant Proc 1977;9:203-8.
15 Müller T, Philipp A, Luchner A, et al. A new miniaturized system for extracorporeal membrane oxygenation in adult respiratory failure. Crit Care 2009;13:R205.
16 Takahashi SM, Garrity ER. The impact of the lung allocation score. Semin Respir Crit Care Med 2010;31:108-14.
17 Rehder KJ, Turner DA, Hartwig MG, et al. Active rehabilitation during extracorporeal membrane oxygenation as a bridge to lung transplantation. Respir Care 2013;58:1291-8.
18 Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242:2193-6.
19 Noah MA, Peek GJ, Finney SJ, et al. Referral to an Extracorporeal Membrane Oxygenation Center and Mortality among Patients with Severe 2009 Influenza a(H1n1). JAMA 2011;306:1659-68.
20 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.
21 Hartwig MG, Appel JZ 3rd, Cantu E 3rd, et al. Improved results treating lung allograft failure with venovenous extracorporeal membrane oxygenation. Ann Thorac Surg 2005;80:1872-9; discussion 1879-80.
22 Hartwig MG, Walczak R, Lin SS, et al. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. Ann Thorac Surg 2012;93:366-71.
23 Suzuki Y, Cantu E, Christie JD. Primary graft dysfunction. Semin Respir Crit Care Med 2013;34:305-19.
24 Hill JD, O'Brien TG, Murray JJ, et al. prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the bramson membrane lung. N Engl J Med 1972;286:629-34.
25 Jackson A, Cropper J, Pye R, et al. Use of Extracorporeal membrane oxygenation as a bridge to primary lung transplant: 3 consecutive, successful cases and a review of the literature. J Heart Lung Transplant 2008;27:348-52.
26 Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
27 Bittner HB, Lehmann S, Rastan A, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery. Ann Thorac Surg 2012;94:942-9; author reply 949-50.
28 Meyers BF, Sundt TM 3rd, Henry S, et al. Selective use of extracorporeal membrane oxygenation is warranted after lung transplantation. J Thorac Cardiovasc Surg 2000;120:20-6.
29 Moreno I, Vicente R, Mir A, et al. Effects of inhaled nitric oxide on primary graft dysfunction in lung transplantation.

Transplant Proc 2009;41:2210-2.
30 Ruberto F, Bergantino B, Testa MC, et al. Low-flow venovenous CO2 removal in association with lung protective ventilation strategy in patients who develop severe progressive respiratory acidosis after lung transplantation. Transplant Proc 2013;45:2741-5.
31 Diaz-Guzman E, Davenport DL, Zwischenberger JB, et al. Lung function and ECMO after lung transplantation. Ann Thorac Surg 2012;94:686-7; author reply 687.
32 Marasco SF, Vale M, Preovolos A, et al. Institution of extracorporeal membrane oxygenation late after lung transplantation - a futile exercise? Clin Transplant 2012;26:E71-7.
33 Aigner C, Jaksch P, Taghavi S, et al. Pulmonary retransplantation: is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant 2008;27:60-5.
34 Shigemura N, Bermudez C, Bhama J, et al. Successful lung retransplantation after extended use of extracorporeal membrane oxygenation as a bridge. Transplant Proc 2011; 43:2063-5.
35 Javidfar J, Brodie D, Iribarne A, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation and recovery. J Thorac Cardiovasc Surg 2012;144:716-21.
36 Haneya A, Philipp A, Mueller T, et al. Extracorporeal circulatory systems as a bridge to lung transplantation at remote transplant centers. Ann Thorac Surg 2011;91:250-5.
37 Mason DP, Thuita L, Nowicki ER, et al. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. J Thorac Cardiovasc Surg 2010;139:765-773.e1.
38 Lang G, Taghavi S, Aigner C, et al. Primary lung transplantation after bridge with extracorporeal membrane oxygenation: a plea for a shift in our paradigms for indications. Transplantation 2012;93:729-36.
39 Bermudez CA, Rocha RV, Zaldonis D, et al. Extracorporeal membrane oxygenation as a bridge to lung transplant: midterm outcomes. Ann Thorac Surg 2011;92:1226-31; discussion 31-2.
40 Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55.
41 Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763-8.
42 Gottlieb J, Warnecke G, Hadem J, et al. Outcome of critically ill lung transplant candidates on invasive respiratory support. Intensive Care Med 2012;38:968-75.
43 Nosotti M, Rosso L, Tosi D, et al. Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. Interact Cardiovasc Thorac Surg 2013;16:55-9.
44 Anile M, Diso D, Russo E, et al. Extracorporeal membrane oxygenation as bridge to lung transplantation. Transplant Proc 2013;45:2621-3.
45 Diaz-Guzman E, Hoopes CW, Zwischenberger JB. The evolution of extracorporeal life support as a bridge to lung transplantation. ASAIO J 2013;59:3-10.
46 Riley JB, Scott PD,Schears GJ. Update on safety equipment for extracorporeal life support (ECLS) circuits. Semin Cardiothorac Vasc Anesth 2009;13:138-45.
47 Haneya A, Philipp A, Foltan M, et al. First experience with the new portable extracorporeal membrane oxygenation system Cardiohelp for severe respiratory failure in adults. Perfusion 2012;27:150-5.
48 Philipp A, Arlt M, Amann M, et al. First experience with the ultra compact mobile extracorporeal membrane oxygenation system Cardiohelp in interhospital transport. Interact Cardiovasc Thorac Surg 2011;12:978-81.
49 Reeb J, Falcoz PE, Santelmo N, et al. Double lumen bi-cava cannula for veno-venous extracorporeal membrane oxygenation as bridge to lung transplantation in non-intubated patient. Interact Cardiovasc Thorac Surg 2012;14:125-7.
50 Smedira NG, Moazami N, Golding CM, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. J Thorac Cardiovasc Surg 2001;122:92-102.
51 Mols G, Loop T, Geiger K, et al. Extracorporeal membrane oxygenation: a ten-year experience. Am J Surg 2000;180:144-54.
52 Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med 2011;365:1905-14.
53 Mair P, Hoermann C, Moertl M, et al. Percutaneous venoarterial extracorporeal membrane oxygenation for emergency mechanical circulatory support. Resuscitation 1996;33:29-34.
54 Bisdas T, Beutel G, Warnecke G, et al. Vascular complications in patients undergoing femoral cannulation for extracorporeal membrane oxygenation support. Ann

Thorac Surg 2011;92:626-31.
55 Foley PJ, Morris RJ, Woo EY, et al. Limb ischemia during femoral cannulation for cardiopulmonary support. J Vasc Surg 2010;52:850-3.
56 Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610-6.
57 Del Sorbo L, Ranieri VM, Keshavjee S. Extracorporeal membrane oxygenation as "bridge" to lung transplantation: what remains in order to make it standard of care? Am J Respir Crit Care Med 2012;185:699-701.

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Review Article

Pediatric heart transplantation—indications and outcomes in the current era

Philip T. Thrush[1,2], Timothy M. Hoffman[1,2]

[1]The Heart Center, Nationwide Children's Hospital, [2]Department of Pediatrics, The Ohio State University, Columbus, OH, USA

Correspondence to: Philip T. Thrush, MD. The Heart Center, Nationwide Children's Hospital, 700 Children's Dr. Columbus, OH 43205, USA. Email: Philip.Thrush@NationwideChildrens.org.

Abstract: Pediatric heart transplantation (HTx) remains an important treatment option in the care of children with end-stage heart disease, whether it is secondary to cardiomyopathy or congenital heart disease (CHD). As surgical outcomes for CHD have improved, the indications for pediatric HTx have had to be dynamic, not only for children with CHD but also for the growing population of adults with CHD. As the field of pediatric HTx has evolved, the outcomes for children undergoing HTx have improved. This is undoubtedly due to the continued research efforts of both single-center studies, as well as research collaboratives such as the International Society for Heart and Lung Transplantation (ISHLT) and the Pediatric Heart Transplant Study (PHTS) group. Research collaboratives are increasingly important in pediatric HTx as single center studies for a limited patient population may not elicit strong enough evidence for practice evolution. Similarly, complications that limit the long term graft survival may occur in a minority of patients thus pooled experience is essential. This review focuses on the indications and outcomes for pediatric HTx, with a special emphasis on studies generated by these research collaboratives.

Keywords: Heart transplantation (HTx); pediatrics; cardiomyopathy; congenital heart defects; graft rejection; graft survival

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Introduction

The field of pediatric heart transplantation (HTx) has progressed significantly since Dr. Adrian Kantrowitz transplanted the heart of a brain dead infant into another infant in 1967 (1). Based on the most recent data, there are now approximately 100 centers performing over 500 pediatric heart transplants yearly worldwide (2). Orthotopic HTx has become an acceptable treatment strategy and the standard of care for end-stage heart disease in children, whether secondary to underlying congenital heart disease (CHD) or cardiomyopathy.

The United Network for Organ Sharing (UNOS) and the International Society for Heart and Lung Transplantation (ISHLT) maintain multicenter databases and collaboratives which have helped forge medical and surgical progress. In addition, the Pediatric Heart Transplant Study (PHTS) was founded in 1991 and is dedicated to the advancement of the science and treatment of children during listing for and following HTx. The purposes of the PHTS are to establish and maintain an international, prospective, event driven database for HTx, to use the database to encourage and stimulate basic and clinical research in the field of pediatric HTx and to promote new therapeutic strategies. The PHTS is unique in that its data entry is event-driven both pre- and post-transplantation, so events such as annual follow-up, development of cardiac allograft vasculopathy (CAV), and rejection are captured in addition to transplantation and death. Through the data provided by these organizations and single-center studies, the field of pediatric heart transplant has and will continue to advance.

Since the initial transplantation performed by Dr. Kantrowitz, advances in surgical technique, understanding of rejection and immunology, immunosuppressive

medications, and treatment for rejection have led to improved outcomes. In addition, improved palliation for complex CHD has helped define those patients who should be considered for pediatric HTx. This article reviews the indications for orthotopic HTx and outcomes in the pediatric population.

Indications

Past guidelines for pediatric HTx have been broadly defined (3,4). Since these guidelines, there have been improvements in surgical palliation for hypoplastic left heart syndrome (HLHS) (5,6), improved understanding of certain diseases such as restrictive cardiomyopathy (RCM) (7,8), extrapolation of heart failure management from adult literature to the pediatric population (9-12), and increasing retransplantation (2)—all of which have led to the need for guideline revision. In addition, adult heart failure has been defined into four stages (13): (I) stage A (at risk); (II) stage B (pre-clinical, asymptomatic); (III) stage C (past/present history of heart failure with symptoms); and (IV) stage D (end-stage heart failure). This staging system has been incorporated into published guidelines for the treatment of pediatric heart failure (14). The American Heart Association commissioned a working group to reassess the indications for pediatric HTx, and the recommendations were published in 2007 (15). These indications are largely based on level C evidence indicating expert clinical opinion (*Table 1*). Repeat transplantation occurs rarely in pediatric populations and, as expected, is associated with a worse outcome as compared to primary transplantation. Indications for repeat transplantation are outlined in *Table 2* and all recommendations are based on level B evidence (data derived from nonrandomized studies).

The improved outcomes in surgical correction and palliation in children with CHD have led to an increasing population of adults with CHD who may develop complications and indications for HTx. This population often warrants increased evaluation of organ systems, including pulmonary function, liver function/cirrhosis, and renal function, given the long-standing effects of palliated CHD on the various organ systems. The published guidelines previously mentioned specifically address the indications and contraindications in this population (15).

The guidelines also outline recommendations where the risk outweighs the benefit and would be considered contraindications to transplantation and retransplantation (15). For example, the efficacy of transplant has not been established in those patients with a history of (I) infection with hepatitis B or C, or human immunodeficiency virus; (II) recent illicit drug or tobacco, or alcohol abuse; and (III) poor psychosocial support and medical non-compliance. Similarly, multisystem organ failure or a progressive and irreversible multisystem disease process precludes HTx. Finally, primary transplant for CHD in which palliative surgery is feasible is not recommended. As for repeat transplantation, there are two main concerns emphasized: (I) retransplantation should not be performed during an ongoing acute allograft rejection episode even in the presence of graft vasculopathy; and (II) retransplantation is not efficacious when performed during the first 6 months after the primary transplant.

There are several notable revisions in these guidelines. For example, RCM is an indication for HTx when associated with reactive pulmonary hypertension. Additionally, due to a limited pediatric donor pool, primary HTx for CHD is not recommended unless there are additional confounding variables such as ventricular dysfunction, significant valvar insufficiency, or severe coronary anomalies. These recommendations also acknowledge the mortality and morbidity associated with pulmonary hypertension, severe valvar insufficiency not amenable to surgery, and protein losing enteropathy in previously repaired or palliated CHD thus translating into indications for HTx.

In addition to the guidelines, certain diagnoses account for the majority of pediatric HTx, including cardiomyopathies and CHD, most notably HLHS and pulmonary atresia with intact ventricular septum. However, other indications for transplant may include refractory arrhythmias and malignancies.

Special considerations/populations

Allosensitization

Allosensitization or highly-sensitized patients are usually defined as having an elevated panel reactive antibody >10%. While human leukocyte antigen (HLA) sensitization is uncommon in patients with cardiomyopathy, it can frequently be seen in patients with CHD who have had prior surgeries. It is accepted that the use of cryopreserved allograft material induces an immune response with the development of both class I and II anti-HLA antibodies and elevated panel reactive antibodies (16,17). In addition to allograft exposure, blood transfusions, mechanical circulatory support, pregnancy, and prior HTx have also been shown to be risk factors for developing anti-HLA

Table 1 Indications for heart transplantation in pediatrics (15)

Indications	Level of evidence
Class I	
Stage D heart failure associated with systemic ventricular dysfunction in pediatric patients with cardiomyopathies or previously repaired/palliated CHD	B
Stage C heart failure associated with severe limitation of exercise and activity. If measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex	C
Stage C heart failure associated with systemic ventricular dysfunction in patients with cardiomyopathies or previously repaired/palliated CHD when heart failure is associated with significant growth failure attributable to the heart disease	B
Stage C heart failure in pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator	C
Stage C heart failure in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension	C
Class IIA	
Stage C heart failure in pediatric heart disease associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future	C
Certain anatomic and physiological conditions likely to worsen the natural history of CHD in infant patients with a functional single ventricle, which can lead to use of heart transplantation as primary therapy, including: (i) severe stenosis (stenoses) or atresia in proximal coronary arteries; (ii) moderate to severe stenosis and/or insufficiency of the AV and/or systemic semilunar valve(s); and (iii) severe ventricular dysfunction	C
Several anatomic and physiological conditions likely to worsen the natural history of previously repaired or palliated CHD in pediatric patients with stage C heart failure that may lead to consideration for heart transplantation without severe systemic ventricular dysfunction, including (i) pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; (ii) severe aortic or systemic AV valve insufficiency that is not considered amenable to surgical correction; (iii) severe arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction; and (iv) persistent protein-losing enteropathy despite optimal medical/surgical therapy	C

CHD, congenital heart disease; AV, atrioventricular.

Table 2 Indications for cardiac retransplantation in pediatrics (15)

Indications	Level of evidence
Class I	
In children with abnormal ventricular function and at least moderate graft vasculopathy	B
Class IIA	
Indicated in children with normal ventricular function and at least moderate graft vasculopathy	B

antibodies. Studies have shown that transplantation in the setting of allosensitization carries increased risk and mortality (18-21). Given this increased risk, some centers may choose not to offer HTx to patients with elevated panel reactive antibody or may result in increased waitlist times.

Alternatively, desensitization (decreasing the circulating anti-HLA antibodies) or prospective/virtual crossmatching may be alternatives to improve outcomes in the setting of allosensitization. Many studies have reported methods to desensitize patients, including administration of

IVIG, plasmapheresis, and use of cyclophosphamide or mycophenolate mofetil (22-25). In addition, newer medications, including rituximab (a monoclonal antibody to CD20) and bortezomib (a proteasome inhibitor directed against plasma cells) have been shown to reduce circulating antibodies (26-29). As opposed to desensitization, prospective crossmatching aims to avoid the potential reaction between the donor and recipient. Unfortunately, prospective crossmatching can be time consuming and requires the presence of both recipient serum and donor cells to perform a direct assessment of the donor-recipient crossmatch. This can be limited by geographical proximity. Alternatively, many advocate for the use of a virtual crossmatch in which the recipient anti-HLA antibody profile is compared to the donor HLA typing to predict a possible crossmatch alleviating the geographic restrictions placed by the direct, prospective crossmatch (30-32).

ABO-incompatible transplantation

Infants currently have the longest waiting time for HTx (33). As such, ABO-incompatible HTx has become increasingly more frequent as a means to decrease potential waiting time. Currently, UNOS guidelines permit ABO-incompatible HTx in children <1 year of age with any isohemagglutinin titer and for infants between 1 and 2 years of age with isohemagglutinin titers ≤1:4. ABO-incompatible eligible infant listing has increased from 0% prior to 2002 to 53% is 2007 (34). Unfortunately, when Almond *et al.* compared ABO-incompatible listed infants to those listed exclusively for ABO-compatible transplantation, there was no difference in waitlist mortality (34). Infants with blood type O were more likely to undergo transplantation by 30 days from listing when listed for ABO-incompatible heart transplant, but this did not hold true for infants listed with either A or B blood types (34). When comparing ABO-incompatible listed infants to those listed for ABO-compatible transplantation, studies have demonstrated they are more likely to require extracorporeal membrane oxygenation (ECMO), mechanical ventilation, and have renal failure, suggesting this listing strategy is still employed in a more ill population which may account for the similar waitlist mortality between the two groups (34,35).

Regardless of the listing strategy, ABO-incompatible heart transplant recipients have similar outcomes to those undergoing ABO-compatible transplantation. Review of the PHTS data demonstrated similar 1-year survival between ABO-incompatible and ABO-compatible infant heart transplants, 82% *vs.* 84%, respectively (35). Comparable results in short-term survival, long-term survival, rejection, and CAV have been borne out by review of the UNOS registry and by Dipchand *et al.* (36,37). In addition to infants and young children, Urschel *et al.* demonstrated that ABO-incompatible HTx can also be performed in older children (up to 90 months in their cohort) and with higher isohemagglutinin titers (up to 1:64 in their cohort) (38). Further studies demonstrating safety and equivalent outcomes could open this opportunity to a much larger population of children.

Fetal listing

Fetal listing for HTx has been proposed as a means to increase the potential window for transplantation. While there are no specific indications for fetal listing, it has historically been utilized when considering primary HTx for left-sided obstructive lesions, such as HLHS. Current UNOS guidelines allow for fetal listing between 32 and 36 weeks gestation after thorough fetal evaluation for viability has been completed, and if the fetus does not undergo transplantation prior to delivery, the waitlist time restarts after delivery as to not disadvantage those listed after birth (39). Fetal listing is currently a rare entity with PHTS registry data indicating showing fetal listing in 46 of the 4,365 (1%) patients between 1993 and 2009 (40). However, there is clearly institutional variation as Pollock-BarZiv *et al.* reported 26 fetal listings of 269 total listings between 1990 and 2006 (this institution is a participating center in the PHTS and is included in the previously mentioned PHTS data) (41). The recent PHTS data demonstrated similar overall waiting times between the fetal and neonatal listing group, but it is worth noting that the patients listed prenatally had a shorter postnatal waiting time (40). Interestingly, in the cohort reported by Pollock-BarZiv *et al.*, two of the fetal listing patients were delivered via cesarean section when a donor became available, and seven of the 26 fetal listings were delisted after delivery (41). The latter statistic poses an intriguing question of whether physicians can truly predict who will require HTx as a fetus, and whether the option of fetal listing by UNOS should persist, as it is currently being considered for elimination.

Outcomes

General outcomes

With collective experience over each era, pediatric HTx outcomes continue to improve. The most recent data from

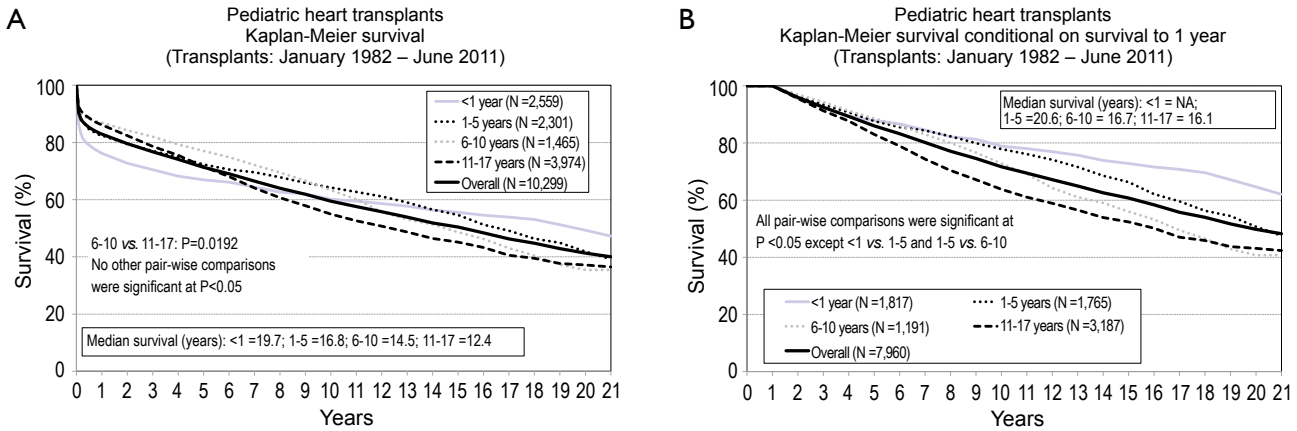

Figure 1 (A) Median patient survival for pediatric heart transplant recipients, birth—17 years of age; (B) median patient survival for pediatric heart transplant recipients conditional on survival to 1 year post-transplant, birth—17 years of age. (ISHLT Registry.)

the ISHLT, including patients from 1982 through June 2011, demonstrates the median survival is 19.7 years for infants, 16.8 years for children ages 1-5 years, 14.5 years for children ages 6-10 years, and 12.4 years for children 11-17 years of age at the time of transplantation (*Figure 1A*) (2). The highest mortality rate remains the during the first year post-transplant, and when accounting for conditional survival during the first year, the median survivals increase to 20.6 years for children ages 1-5 years, 16.7 for children ages 6-10 years, and 16.1 years for children 11-17 years of age (*Figure 1B*) (2). The decreasing median survival in older age groups is likely multifactorial and related to several factors including, the relative immature immune system in the infants and lack of preformed antibodies, sensitization in the older children due to surgical repair and palliation for CHD, and risk-taking behaviors such as medication non-compliance in older children. Additional factors are discussed below. Recent analysis of the PHTS registry demonstrated an overall survival of 83% at 5 years after transplantation in the most recent era [2005-2009] (42). While these outcome data are limited to 5 years of follow-up, a significant increase in survival was noted at 5 years post-transplant between the most recent era and those transplanted between 2000 and 2004, 83% *vs.* 76%, respectively (42). This study also assessed many variables that affect outcomes, many of which are outlined in this review.

Donor variables have also been shown to affect pediatric heart transplant outcomes. Factors previously thought to negatively impact post-transplant survival, such as donor cause of death, need for inotropic support, and cardiopulmonary resuscitation, have been recently shown to have no significant impact on outcomes (43). Gender mismatch between the donor and recipient has also been shown not to affect the post-transplant survival (44). However, recent analysis of the PHTS registry did demonstrate that longer ischemic times (>300 min) adversely impacted survival at 1 year but not overall survival, and the effect of ischemic time was a greater factor for patients >10 years of age (43). While the donor ischemic time is dependent upon donor variables, e.g., proximity to the recipient, it can also be dependent upon recipient variables, including complex CHD and the number of prior sternotomies.

Despite improved post-transplantation outcomes and advances in cardiovascular support for those awaiting transplantation, a relative shortage of organs persists, and waitlist mortality remains an important topic. Analysis of the United States Scientific Registry of Transplant Recipients (SRTR) has shown a waitlist mortality of 17% for pediatric HTx (45), and others have shown that waitlist mortality is as high as 23% by 6 months after listing in the highest risk group—infants (33). In addition, several factors have been found to be associated with increased waitlist mortality, including the need for ECMO or mechanical ventilation, status 1A listing, diagnosis of CHD (with or without prior surgery), the need for dialysis, weight <3 kilograms, and non-white race (33,45,46). In 2006, changes were made to the organ allocation system resulting in broader regional sharing, and this has been shown to decrease the risk of waitlist mortality or becoming too ill to transplant by 17% in the adult population but has not been studied in pediatric HTx (47). Despite multiple studies demonstrating risk factors for waitlist mortality in pediatric patients, the current

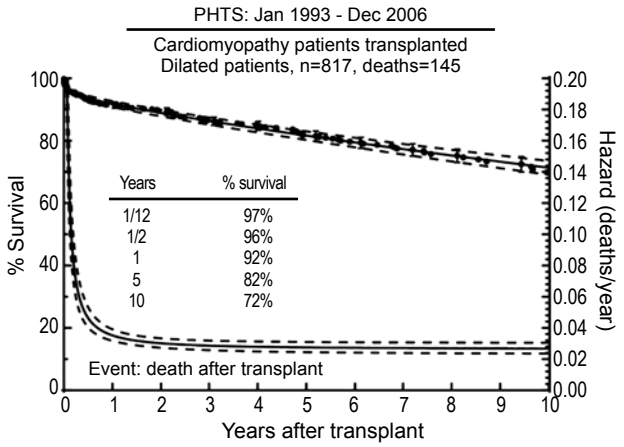

Figure 2 Survival and hazard curves for death after heart transplant for patients with dilated cardiomyopathy included in the Pediatric Heart Transplant Study Registry (PHTS Registry).

allocation algorithm for pediatric HTx remains imperfect and does not distinguish between a single high-dose inotrope and more aggressive means of support, such as mechanical circulatory support or mechanical ventilation. However, there is ongoing debate regarding the current allocation system with potential changes to more closely mirror the adult allocation algorithm looming in the future. Ideally, revising the allocation system to reflect the risk factors above would result in improved waitlist mortality for children awaiting HTx, but follow-up and review would be necessary if these changes manifest.

Specific diseases and their outcomes

Cardiomyopathy

Cardiomyopathy is the most common indication for pediatric HTx, ranging from 41% of patients <1 year of age to 65% of patients between 11 and 17 years of age (2), and has become an increasing indication for pediatric HTx over the past three decades (2,48). This group is comprised of dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and RCM. Some patients may also manifest a mixed phenotype with characteristics of both RCM and DCM or HCM.

Dilated cardiomyopathy (DCM)

The incidence of DCM is 0.58 cases per 100,000 children and accounts for over 50% of cardiomyopathies in the U.S (49). Based on the Pediatric Cardiomyopathy Registry (PCMR) data, the majority of pediatric DCM cases (66%) are idiopathic but may be due to myocarditis, neuromuscular disease, or genetic causes (50). Neuromuscular disorders and metabolic disorders may have decreased life expectancies or survival rates lower than their freedom from transplantation which must be factored when assessing for HTx. The freedom from death or transplantation at 1 and 5 years after DCM diagnosis was 69% and 54%, respectively, and risk factors for death or transplantation included age >6 years or congestive heart failure at presentation and lower left ventricular echocardiographic fractional shortening (50). However, myocarditis as an etiology for DCM was associated with decreased risk compared to idiopathic DCM (50).

Analysis of the PHTS registry demonstrated relatively low waitlist mortality (11%) for patients with DCM listed for transplantation, but factors including history of mechanical ventilation and presence of arrhythmias did increase the risk of death while awaiting transplantation (51). In addition, a recent study utilizing both PCMR and PHTS registries found that older age at diagnosis, in addition to ventilator use, was an additional risk factor for death on the waitlist (52). Singh *et al.* demonstrated excellent short-term post-transplant survival for patients with DCM with 30-day and 1-year survivals of 98% and 94%, respectively (53). Based on the most recent PHTS data, 74% of pediatric patients with DCM listed for HTx ultimately underwent transplant, and their 10-year post-transplant survival was 72% (*Figure 2*) (51). Risk factors associated with death post-transplantation included black race, older age, mechanical ventilation at transplant, longer ischemic time, and earlier era of transplantation (51). The outcomes for patients with DCM post-transplant were noted to better than those for other forms of pediatric cardiomyopathy (51,54,55).

Hypertrophic cardiomyopathy (HCM)

The incidence of HCM is 0.47 cases per 100,000 children and accounts for 42% of pediatric cardiomyopathy (49). HCM may be idiopathic, familial, associated with neuromuscular disorders, or associated with certain syndromes such as Noonan's-spectrum syndromes (e.g., Noonan's syndrome, LEOPARD syndrome, Costello syndrome) and Beckwith-Weidemann syndrome. While it is well-accepted that these patients are at risk for arrhythmias and sudden cardiac death, a recent study demonstrated that heart failure deaths were at least as common as sudden cardiac death in pediatric HCM patients (56). HCM is an infrequent etiology for pediatric HTx, accounting for 5-6% of transplantations (54,57). While it makes up a minority of pediatric HTx, several risk factors have been identified those at increased risk for death or transplantation, including age <1 year old, low weight, lower left ventricular fractional

shortening, or higher end-diastolic left ventricular posterior wall or septal thickness at the time of diagnosis (58,59). In children with HCM, abnormal blood pressure response to exercise has also shown to be predictive of poor outcomes (56). In a recent large retrospective study from the PCMR, which included 1,085 children with HCM, rates of death or HTx were highest in those populations with inborn errors of metabolism (57% at 2 years from diagnosis) and with mixed phenotypes (45% at 2 years for HCM/DCM and 38% at 2 years for HCM/RCM) (58). This is further supported by a recent study that demonstrated restrictive physiology (defined by echocardiographic parameters) in the presence of HCM conferred a 3.5-fold increased risk of hospitalization and 5.7-fold increased risk of death or transplantation (60). The risk of death or HTx also increases with the presence of increasing number of risk factors (58).

The waitlist mortality for patients with HCM is higher compared to those with DCM (14% *vs.* 11%), and identified risk factors for waitlist mortality in this cohort include UNOS status 1 and younger age (51,54). Waitlist mortality has been shown to be consistently higher in infants with HCM compared to other age groups with HCM (54,61). The 10-year survival post-transplant for patients with HCM in the PHTS registry is 47% which is significantly less than both the DCM cohort and the non-cardiomyopathy cohort in the registry, 72% and 63% respectively (51,54).

Restrictive cardiomyopathy (RCM)

RCM is the rarest form of pediatric cardiomyopathy and is characterized by "normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function." (62). The incidence of RCM is 0.03-0.04 cases per 100,000 children (49,63) and accounts for 4.5% of pediatric cardiomyopathies (64). Analysis of the PCMR database demonstrated approximately 1/3 of patients with RCM had a mixed phenotype (RCM/HCM) (64). Historically, pediatric patients with RCM have been shown to have a poor prognosis with a mortality rate of 63% at 3 years from diagnosis (65) and 75% at 6 years from diagnosis (66). Syncope and evidence of ischemia are poor prognostic signs (67). This poor prognosis, along with the risk of progressive, irreversible pulmonary hypertension, thromboembolic events, sudden death, and the limited medical treatment options, has led to some centers listing for HTx at the time of diagnosis. This has skewed the assessment of the natural history of the disease, but recent review of the PCMR demonstrated the cumulative incidence of death was 20% at 5 years from diagnosis in the pure RCM group and 28% at 5 years from diagnosis in the RCM/HCM group (64). In addition, the cumulative incidence of HTx was 58% at 5 years from diagnosis in the pure RCM group and 30% at five years from diagnosis in the RCM/HCM group (64). Given the potential risks in this population, close observation is warranted and early listing for HTx should be considered.

Patients with RCM listed for HTx had 10% waitlist mortality, and identified risk factors for waitlist mortality were similar to the other cardiomyopathy cohorts and include younger age, ventilator dependence, UNOS status 1, ECMO, ventricular assist device, intra-aortic balloon pump, and inotrope use (55). The 10-year survival outcome for patients with RCM was better than those patients with HCM, but not as good as those with DCM, 63% *vs.* 47% *vs.* 72% respectively (51,54,55). Risk factors for death post-transplant included earlier era of transplant in the early phase and older age (10 *vs.* 5 years) and black race are in the constant phase (55).

Congenital heart disease (CHD)

As previously discussed, advances in surgical technique and outcomes continue to redefine the population of CHD patients undergoing HTx. This population includes infants with both unrepaired and palliated complex CHD and adults with palliated CHD who either have failed palliations or ventricular dysfunction. While ISHLT data continue to show cardiomyopathy is the most frequent indication for pediatric heart transplant worldwide (2), large-volume center data in the United States demonstrates increasing incidence of transplantation for CHD. Voeller *et al.* reported 57% (173/307) of their HTxs were for CHD, and of those, 80% had single-ventricle anatomy (48). In addition, for their most recent cohort [2002-2009], the most common indication for HTx in patients with CHD was failed single-ventricle palliation (48).

This is particularly relevant in patients with HLHS with several studies demonstrating improved outcomes in staged palliations for a disease that was previously considered frequently for primary transplantation (5,6,68). These improved outcomes have resulted in (I) decreased utilization of primary transplant as a treatment for HLHS (69,70); (II) utilization of transplantation at most institutions for patients with HLHS and complications such as significantly depressed right ventricular function or significant tricuspid valve regurgitation; and (III) an increase in the number

of patients with HLHS with prior surgical interventions proceeding to HTx as many of these patients have had some form of prior palliation. In addition, the success with HLHS has led to utilization of HTx in other univentricular conditions such as pulmonary atresia with intact ventricular septum associated with right-ventricular dependent coronary circulation and ostial stenosis/atresia as well as complex heterotaxy syndromes (71-74). While most institutions proceed with palliation as an initial first step for complex CHD with univentricular physiology, Auerbach *et al.* demonstrated a better graft survival (median graft survival 18 years compared to 8 years) and decreased incidence of acute rejection in those patients with univentricular hearts that had not undergone prior surgical procedures (75). Despite this, many patients will require some form of palliation, especially neonates, in order to bridge to HTx given current wait times.

In addition to risk of transplant early in life, these patients are also at risk for transplantation following the superior cavopulmonary anastomosis (Glenn procedure) or following total cavopulmonary anastomosis (Fontan procedure). Of particular interest in recent years is the "failed-Fontan" patient. A failed-Fontan can manifest as systolic ventricular dysfunction, alterations in the structure and function of the pulmonary vascular bed, significant atrioventricular valve insufficiency, arrhythmia, plastic bronchitis, or protein-losing enteropathy (PLE) (76-80). Fontan conversion with arrhythmia surgery has been utilized in select patients (81-83). While the staged palliation approach, including the Fontan procedure, have increased transplant-free survival, it can increase risk for future transplant given the potential of allosensitization which has portended a worse outcome (84). In addition, UNOS status 1 at listing, ventilator support, and a time interval of less than 6 months from the initial Fontan palliation have been shown to be risk factors for death after listing for transplant in the failed-Fontan population (70). For those patients who develop plastic bronchitis, transplant may be considered given the risk for life-threatening events. While literature is limited, recent review of the PHTS data demonstrated these patients may have an increased short-term mortality (70% survival at 30 days) but comparable long-term outcomes by 5 years post-transplantation (85). For those with PLE, HTx has provided complete resolution of PLE (86-88). Unfortunately, PLE may recur in this patient population group suggesting they may be more sensitive to complications such as restrictive physiology in the setting of CAV, but repeat transplantation has also been shown to be potentially curative (89).

Post-transplantation complications

Rejection

Rejection remains one of the main post-transplant complications limiting long-term graft survival, and it can occur at any point after placement of the graft. Data from the PHTS has shown that incidence and prevalence of rejection has decreased over time (study period January 1993-December 2005), but the incidence of rejection with hemodynamic compromise and mortality from rejection have remained stable (90). In the most recent era (July 2008-June 2012), 22% of children will experience rejection during the first year post-transplant, and this is decreased from 34% from the preceding era (July 2004 - June 2008) (*Figure 3*) (2). Data from the PHTS show demonstrate 64% of patients were free of rejection in the first year (36% of patients experiencing rejection) and a 5-year freedom from rejection of 52% (*Figure 4*) (42). This difference is likely related to the difference in how rejection is classified between the two databases. In addition, treated rejection during the first year post-transplantation has been shown to significantly decrease long-term survival (88% *vs.* 80% patient survival at 5 years post-transplant) (2). Additional data from the PHTS have shown that late rejection, occurring >1 year after transplant, has decreased in the recent era, but there has been no decrease in the association between late rejection and CAV and mortality (91). Older age, African-American race, and elevated PRA have been shown repeatedly to be risk factors for rejection (92-95), and early rejection has been shown to be a risk factor for late rejection (91). Not surprisingly, non-adherence has also been shown to be a risk factor for late-rejection (96).

Interestingly, while the use of induction immunosuppression following HTx has increased, there has been no significant change in the amount of rejection. According to the most recent data from the ISHLT, 58% of children receiving a heart transplant between January 2001 and June 2012 received some form of induction immunosuppression, with approximately two-thirds of those receiving a polyclonal antilymphocyte or antithymocyte globulin and approximately one-third receiving an IL-2 receptor antagonist. This has increased from the data reported in 2003, where approximately 40% of children received some form of induction (97). In the most recent ISHLT Registry report, there were no differences in the percentages of patients experiencing rejection comparing induction, whether being a polyclonal or IL-2 receptor antagonist, to those who did not receive induction immunosuppression (2).

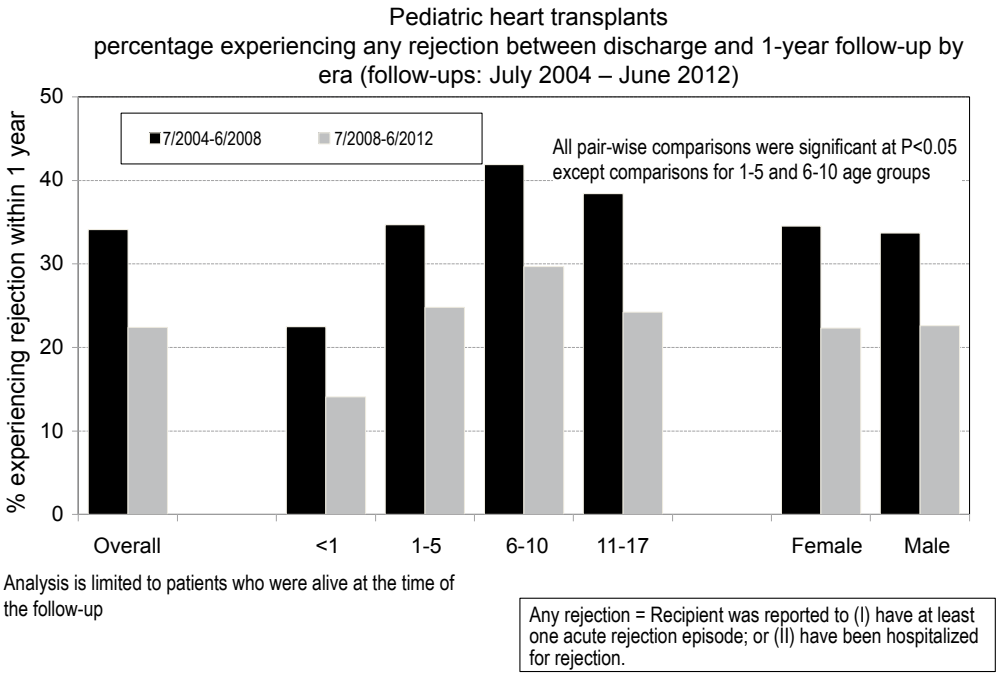

Figure 3 Percentage of pediatric heart transplant recipients experiencing any rejection between discharge and 1-year follow-up based on era (ISHLT Registry).

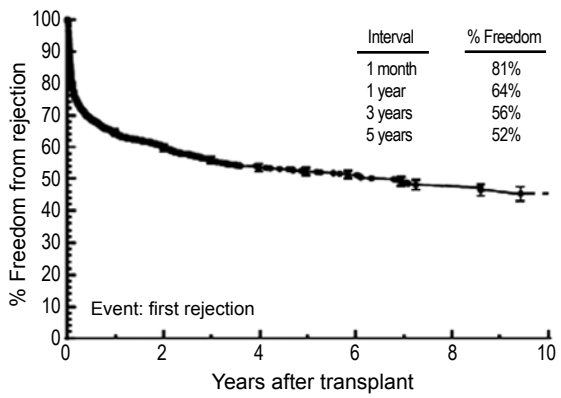

Figure 4 Freedom from first episode of rejection [2000-2009] (PHTS Registry).

Maintenance immunosuppression has also impacted the incidence of rejection. In the most recent ISHT Registry report, tacrolimus has been shown to be associated with a lower incidence of rejection (when assessing for both any episode of rejection and for only treated episodes of rejection) compared to cyclosporine, whether with or without induction immunosuppression (2). A similar picture is seen when comparing tacrolimus and cyclosporine combined with either mycophenolic acid or mycophenolate mofetil, but no difference was noted when comparing tacrolimus to cyclosporine when combined with azathioprine (2).

Infections

Infection remains an important cause of morbidity and mortality and accounts for approximately 12% of deaths during the first year following transplantation (2). Immunosuppression to prevent rejection renders the host potentially susceptible to infection, particularly opportunistic infections. These infections can occur across all ages, but one single-center study demonstrated that infants were more likely to experience more severe and chronic infections (98). In current practice, most patients receive antibiotic prophylaxis, including both bacterial and viral [cytomegalovirus (CMV)] prophylaxis at least for a period of time.

Common bacterial infections include *Staphylococcus* species, *Pseudomonas* species, and *Enterobacter cloacae*, which are commonly encountered in the early post-transplant period and may be nosocomial (99,100). *Streptococcus* pneumoniae becomes a more common source of pulmonary and hematologic infection 1 year after transplantation

(101,102). Unfortunately, various studies have shown that pediatric transplant recipients mount a lower response to pneumococcal vaccination (103,104).

CMV is the most common viral infection and has a peak hazard occurring 6-8 weeks after transplantation (99). While CMV can cause disease directly, it has also been show to play a role in acute rejection, graft vasculopathy, and post-transplant lymphoproliferative disease (PTLD) (105-107). Those patients who are CMV seronegative and receive a seropositive donor organ are the highest risk of developing infection. As such, prophylactic antiviral treatment, including ganciclovir, valganciclovir, or acyclovir, is recommended for 3 months in the high-risk recipient and 1-3 months for all other recipients (108). Other common viral infections include Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV), and influenza viruses. EBV is a human herpes virus that causes a spectrum of disease, ranging from mononucleosis to PTLD, which will be discussed later (109). HSV typically affects the skin and oral mucosa but can involve other organs such as the lungs. This can be related to primary infection or reactivation after transplantation. Varicella infection post-transplantation has been shown to be nearly equally divided between both primary infection and reactivation (110). Acyclovir treatment is indicated for treatment of varicella infection, and administration of varicella zoster immunoglobulin within 48 hours of exposure is indicated for prevention.

Fungal infections are relatively uncommon following pediatric HTx. Based on PHTS registry data, fungal infections account for 6.8% of post-transplant infections (111). Most of these infections are attributable to *Candida* species followed by *Aspergillus*, while *Pneumocystis jiroveci* accounted for 13% of all fungal infections (111). The PHTS registry demonstrated *P. jiroveci* infection occurred in 1% of pediatric heart transplant recipients (112). Risk factors identified for fungal infections after multivariate analysis included previous surgery and mechanical support at the time of transplantation (111). Based on PHTS data, invasive fungal infections carry a mortality rate of 49% with all deaths occurring within the first 6 months following transplantation (111). *Pneumocystis jiroveci* has been shown to have a decreased mortality compared to other fungal infections (112). Current guidelines recommend prophylaxis against *P. jiroveci* with trimethoprim/sulfamethoxazole for 3-24 months (108).

Cardiac allograft vasculopathy (CAV)

CAV remains one of the leading causes of mortality and allograft loss in late survivors following pediatric HTx affecting 34% of patients by 10 years post-transplantation (2). Utilizing the UNOS registry, Kobayashi *et al.* demonstrated the incidence of CAV at 10 and 15 years post-transplantation was 25% and 54%, respectively (113). CAV typically manifests as a loss of distal coronary vasculature via intimal and medial proliferation and results in diastolic dysfunction and graft failure. The most recent ISHLT registry data show no difference in freedom from CAV based on the use of induction immunosuppression or the choice of calcineurin inhibitor (2). Identified risk factors for the development of CAV include ages 1-18 years at the time of transplant (but not infants), re-transplantation, recipient African-American race, and donor cigarette use (113). Currently, the gold standard for diagnosis of CAV is coronary angiography, although studies utilizing intravascular ultrasound and rotational angiography have been published (114-117). Cardiac magnetic resonance imaging and computed tomography have yet to be validated in children. Current medical management for CAV is limited. The introduction of m-TOR inhibitors, rapamycin and everolimus, have shown promise in slowing the progression of CAV and potentially preventing the development of CAV compared to azathioprine, but azathioprine has been predominantly replaced by mycophenolic acid/mycophenolate mofetil in current practice (118,119). However, given these studies, it is not unusual to either replace mycophenolate mofetil with an m-TOR inhibitor or add an m-TOR inhibitor to the medical regimen. In addition to m-TOR inhibitors, statins, particularly pravastatin, have also been shown to be beneficial in the treatment and potential prevention of CAV and safe for use in pediatrics (120-123). For the patient with a focal, proximal stenosis, percutaneous coronary stent placement may be indicated and has been shown to be safe in a pediatric population (124). For severe disease or progressive disease, treatment is limited to retransplantation. Following the diagnosis of CAV, the 1- and 3-year graft survivals are 66-77% and 52-60%, respectively, across the studied age groups (2).

Malignancy and PTLD

Malignancy remains a relatively uncommon complication post-transplant. The incidence of malignancy in the ISHTL registry at 5 and 10 years following transplantation is 5% and 9.5%, respectively, with PTLD making up the vast majority (2). The incidence is similar in the PHTS registry with 6% and 10% of patients developing PTLD at 5 and

10 years (125). PTLD can manifest in variable forms ranging from benign lymphoid hyperplasia to aggressive lymphoma. PTLD is typically an abnormal proliferation of B cells, and it is most often related to EBV (up to 87% of cases), but this need not be the case (109). PTLD most commonly arises from the gastrointestinal tract or lungs, but can manifest anywhere lymphoid tissue exists (109). In some studies, the use of induction immunosuppression has not been found to correlate with the development of PTLD (2,126) while the use and duration of induction immunosuppression has been shown to be risk factor in other studies (127-129). However, donor-recipient EBV mismatch and EBV viral load have been shown to be risk factors for the development of PTLD (128,129). Treatment for PTLD is dependent upon the histology, i.e., monomorphic or polymorphic. Initial treatment has historically included reduced immunosuppression, including potential discontinuation of anti-metabolites and significant reduction in calcineurin inhibitor. Immunosuppression reduction alone has been shown to lead to long-term disease remission in 40-86% of cases of PTLD in pediatric patients (130-132). Unfortunately, reduction of immunosuppression may lead to potential rejection as demonstrated in a PHTS study in which 61% of patients developed acute cellular rejection in the first 6 months following diagnosis of PTLD (109). Thus, other therapies have been investigated and employed especially in those patients in whom the risk of lowering immunosuppression outweighs the potential benefit. Rituximab, a chimeric mouse/human monoclonal antibody against CD20, has been shown to be effective in the treatment of PTLD (133,134). In some cases, particularly monomorphic PTLD, chemotherapy is warranted. Despite treatment, survival after diagnosis of PTLD is poor 75% of patients surviving 1 year and 67% of patients surviving 5 years (109).

Renal disease

Renal dysfunction is typically a consequence of nephrotoxicity secondary to calcineurin inhibitors. At 10 years post-transplantation, severe renal dysfunction, defined as either creatinine >2.5 mg/dL, dialysis, or renal transplant, is seen in 4% of patients transplanted as infants, 5% of patients transplanted between 1 and 5 years of age, 16% of patients transplanted between 6 and 10 years of age, and 14% of patients transplanted between 11 and 17 years of age (2). However, analysis of the PHTS data found that 71% of patients 5 years post-transplant and 57% of patients 10 years post-transplant had renal dysfunction defined as an estimated GFR <60 mL/min/1.73 m^2 (135). Based on the ISHLT registry, there is no difference between the use of tacrolimus or cyclosporine in the development of severe renal dysfunction (2). Risk factors for development of late renal dysfunction include earlier era of HTx, African-American race, and rejection with hemodynamic compromise in the first year post-transplant, but renal function at the time of transplant was not found to be a risk factor (135). In the PHTS cohort, 1.4% of patients progressed to require chronic dialysis or renal transplantation (135).

Retransplantation

Given the complications above, all patients undergoing HTx will need to be considered for retransplantation. For the last decade, retransplantation has accounted from approximately 25-30% of pediatric heart transplants reported to the ISHLT (2). Retransplantation is more common in the older pediatric population with <1% of infants undergoing retransplantation, whereas retransplantation accounts for 9% of transplants in children 11-17 years of age based on the most recent ISHLT data (2). CAV and graft failure remain the most common causes of death (2), and CAV was the most common indication for retransplantation when reviewing both UNOS and PHTS data (136,137). Both of the aforementioned studies have demonstrated inferior survival compared to primary transplantation at all-time points. In particular, the 1-year survival for both studies is ~80%, and the PHTS data demonstrated a 5-year survival of 60% while the UNOS data found a 53% survival at 5 years (136,137). Also, both studies found that a shorter time frame from primary transplantation was a risk factor of decreased survival after retransplantation (136,137). Mahle *et al.* also found that mechanical ventilation prior to retransplantation was a risk factor for decreased survival (136). Given the limited organ supply, it is worth considering these factors when evaluating children for repeat transplantation.

Conclusions

Pediatric HTx has continued to evolve since first performed in 1967. With advances in surgical strategies and medical therapies, the outcomes for pediatric heart transplant recipients have continually improved. While significant post-transplant complications remain, including rejection, infection, malignancy, and CAV, heart transplant remains a therapeutic option to improve both the quality and quantity

of life for pediatric patients. With continued research from individual institutions and large registries, including the ISHLT and PHTS, collective experience and understanding of pediatric heart transplant will translate to practice evolution which will ultimately decrease morbidity and enhance patient and graft survival.

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References

1. Kantrowitz A, Haller JD, Joos H, et al. Transplantation of the heart in an infant and an adult. Am J Cardiol 1968;22:782-90.
2. Dipchand AI, Kirk R, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Heart Transplantation Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:979-88.
3. Mudge GH, Goldstein S, Addonizio LJ, et al. 24th Bethesda conference: Cardiac transplantation. Task Force 3: Recipient guidelines/prioritization. J Am Coll Cardiol 1993;22:21-31.
4. Costanzo MR, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation 1995;92:3593-612.
5. Mahle WT, Spray TL, Wernovsky G, et al. Survival after reconstructive surgery for hypoplastic left heart syndrome: A 15-year experience from a single institution. Circulation 2000;102:III136-41.
6. Tweddell JS, Hoffman GM, Mussatto KA, et al. Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. Circulation 2002;106:I82-9.
7. Kimberling MT, Balzer DT, Hirsch R, et al. Cardiac transplantation for pediatric restrictive cardiomyopathy: presentation, evaluation, and short-term outcome. J Heart Lung Transplant 2002;21:455-9.
8. Russo LM, Webber SA. Idiopathic restrictive cardiomyopathy in children. Heart 2005;91:1199-202.
9. Bruns LA, Chrisant MK, Lamour JM, et al. Carvedilol as therapy in pediatric heart failure: an initial multicenter experience. J Pediatr 2001;138:505-11.
10. Azeka E, Franchini Ramires JA, et al. Delisting of infants and children from the heart transplantation waiting list after carvedilol treatment. J Am Coll Cardiol 2002;40:2034-8.
11. Shaddy RE, Curtin EL, Sower B, et al. The Pediatric Randomized Carvedilol Trial in Children with Heart Failure: rationale and design. Am Heart J 2002;144:383-9.
12. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298:1171-9.
13. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.
14. Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. J Heart Lung Transplant 2004;23:1313-33.
15. Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;115:658-76.
16. Hawkins JA, Breinholt JP, Lambert LM, et al. Class I and class II anti-HLA antibodies after implantation of cryopreserved allograft material in pediatric patients. J Thorac Cardiovasc Surg 2000;119:324-30.
17. O'Connor MJ, Lind C, Tang X, et al. Persistence of anti-human leukocyte antibodies in congenital heart disease late after surgery using allografts and whole blood. J Heart Lung Transplant 2013;32:390-7.
18. Wright EJ, Fiser WP, Edens RE, et al. Cardiac transplant outcomes in pediatric patients with pre-formed anti-human leukocyte antigen antibodies and/or positive retrospective crossmatch. J Heart Lung Transplant 2007;26:1163-9.
19. Mahle WT, Tresler MA, Edens RE, et al. Allosensitization and outcomes in pediatric heart transplantation. J Heart Lung Transplant 2011;30:1221-7.
20. Eckman PM. Immunosuppression in the sensitized

heart transplant recipient. Curr Opin Organ Transplant 2010;15:650-6.
21. Holt DB, Lublin DM, Phelan DL, et al. Mortality and morbidity in pre-sensitized pediatric heart transplant recipients with a positive donor crossmatch utilizing peri-operative plasmapheresis and cytolytic therapy. J Heart Lung Transplant 2007;26:876-82.
22. Ratkovec RM, Hammond EH, O'Connell JB, et al. Outcome of cardiac transplant recipients with a positive donor-specific crossmatch--preliminary results with plasmapheresis. Transplantation 1992;54:651-5.
23. Clark B, Cole JY, Wortley A, et al. Intravenous immunoglobulin-induced panel reactive antibody A reduction: not all preparations are created equal. Transplantation 2003;75:242-5.
24. Itescu S, Burke E, Lietz K, et al. Intravenous pulse administration of cyclophosphamide is an effective and safe treatment for sensitized cardiac allograft recipients. Circulation 2002;105:1214-9.
25. Leech SH, Lopez-Cepero M, LeFor WM, et al. Management of the sensitized cardiac recipient: the use of plasmapheresis and intravenous immunoglobulin. Clin Transplant 2006;20:476-84.
26. Balfour IC, Fiore A, Graff RJ, et al. Use of rituximab to decrease panel-reactive antibodies. J Heart Lung Transplant 2005;24:628-30.
27. Trivedi HL, Terasaki PI, Feroz A, et al. Abrogation of anti-HLA antibodies via proteasome inhibition. Transplantation 2009;87:1555-61.
28. Morrow WR, Frazier EA, Mahle WT, et al. Rapid reduction in donor-specific anti-human leukocyte antigen antibodies and reversal of antibody-mediated rejection with bortezomib in pediatric heart transplant patients. Transplantation 2012;93:319-24.
29. Patel J, Everly M, Chang D, et al. Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. J Heart Lung Transplant 2011;30:1320-6.
30. Zangwill SD, Ellis TM, Zlotocha J, et al. The virtual crossmatch--a screening tool for sensitized pediatric heart transplant recipients. Pediatr Transplant 2006;10:38-41.
31. Zangwill S, Ellis T, Stendahl G, et al. Practical application of the virtual crossmatch. Pediatr Transplant 2007;11:650-4.
32. Chang D, Kobashigawa J. The use of the calculated panel-reactive antibody and virtual crossmatch in heart transplantation. Curr Opin Organ Transplant 2012;17:423-6.
33. Mah D, Singh TP, Thiagarajan RR, et al. Incidence and risk factors for mortality in infants awaiting heart transplantation in the USA. J Heart Lung Transplant 2009;28:1292-8.
34. Almond CS, Gauvreau K, Thiagarajan RR, et al. Impact of ABO-incompatible listing on wait-list outcomes among infants listed for heart transplantation in the United States: a propensity analysis. Circulation 2010;121:1926-33.
35. Henderson HT, Canter CE, Mahle WT, et al. ABO-incompatible heart transplantation: analysis of the Pediatric Heart Transplant Study (PHTS) database. J Heart Lung Transplant 2012;31:173-9.
36. Patel ND, Weiss ES, Scheel J, et al. ABO-incompatible heart transplantation in infants: analysis of the united network for organ sharing database. J Heart Lung Transplant 2008;27:1085-9.
37. Dipchand AI, Pollock BarZiv SM, Manlhiot C, et al. Equivalent outcomes for pediatric heart transplantation recipients: ABO-blood group incompatible versus ABO-compatible. Am J Transplant 2010;10:389-97.
38. Urschel S, Larsen IM, Kirk R, et al. ABO-incompatible heart transplantation in early childhood: an international multicenter study of clinical experiences and limits. J Heart Lung Transplant 2013;32:285-92.
39. http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_4.pdf
40. Conway J, Chrisant MR, West LJ, et al. Outcomes of fetal listed patients awaiting heart transplantation. Pediatr Transplant 2013;17:653-60.
41. Pollock-Barziv SM, McCrindle BW, West LJ, et al. Waiting before birth: outcomes after fetal listing for heart transplantation. Am J Transplant 2008;8:412-8.
42. Dipchand AI, Kirk R, Mahle WT, et al. Ten yr of pediatric heart transplantation: a report from the Pediatric Heart Transplant Study. Pediatr Transplant 2013;17:99-111.
43. Conway J, Chin C, Kemna M, et al. Donors' characteristics and impact on outcomes in pediatric heart transplant recipients. Pediatr Transplant 2013;17:774-81.
44. Tosi L, Federman M, Markovic D, et al. The effect of gender and gender match on mortality in pediatric heart transplantation. Am J Transplant 2013;13:2996-3002.
45. Almond CS, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the United States. Circulation 2009;119:717-27.
46. Jeewa A, Manlhiot C, Kantor PF, et al. Risk factors for mortality or delisting of patients from the pediatric heart transplant waiting list. J Thorac Cardiovasc Surg 2014;147:462-8.
47. Singh TP, Almond CS, Taylor DO, et al. Decline in heart

transplant wait list mortality in the United States following broader regional sharing of donor hearts. Circ Heart Fail 2012;5:249-58.
48. Voeller RK, Epstein DJ, Guthrie TJ, et al. Trends in the indications and survival in pediatric heart transplants: a 24-year single-center experience in 307 patients. Ann Thorac Surg 2012;94:807-15; discussion 815-6.
49. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647-55.
50. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006;296:1867-76.
51. Kirk R, Naftel D, Hoffman TM, et al. Outcome of pediatric patients with dilated cardiomyopathy listed for transplant: a multi-institutional study. J Heart Lung Transplant 2009;28:1322-8.
52. Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation 2012;126:1079-86.
53. Singh TP, Almond CS, Piercey G, et al. Current outcomes in US children with cardiomyopathy listed for heart transplantation. Circ Heart Fail 2012;5:594-601.
54. Gajarski R, Naftel DC, Pahl E, et al. Outcomes of pediatric patients with hypertrophic cardiomyopathy listed for transplant. J Heart Lung Transplant 2009;28:1329-34.
55. Zangwill SD, Naftel D, L'Ecuyer T, et al. Outcomes of children with restrictive cardiomyopathy listed for heart transplant: a multi-institutional study. J Heart Lung Transplant 2009;28:1335-40.
56. Decker JA, Rossano JW, Smith EO, et al. Risk factors and mode of death in isolated hypertrophic cardiomyopathy in children. J Am Coll Cardiol 2009;54:250-4.
57. Canter CE, Naftel DC. Recipient characteristics. Heart transplantation. In: Fine R, Webber S, Harmon W, et al. eds. Pediatrc solid organ transplantation. Oxford (UK): Blackwell, in press.
58. Lipshultz SE, Orav EJ, Wilkinson JD, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet 2013;382:1889-97.
59. Nugent AW, Daubeney PE, Chondros P, et al. Clinical features and outcomes of childhood hypertrophic cardiomyopathy: results from a national population-based study. Circulation 2005;112:1332-8.
60. Maskatia SA, Decker JA, Spinner JA, et al. Restrictive physiology is associated with poor outcomes in children with hypertrophic cardiomyopathy. Pediatr Cardiol 2012;33:141-9.
61. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation 2007;115:773-81.
62. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807-16.
63. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003;348:1639-46.
64. Webber SA, Lipshultz SE, Sleeper LA, et al. Outcomes of restrictive cardiomyopathy in childhood and the influence of phenotype: a report from the Pediatric Cardiomyopathy Registry. Circulation 2012;126:1237-44.
65. Cetta F, O'Leary PW, Seward JB, et al. Idiopathic restrictive cardiomyopathy in childhood: diagnostic features and clinical course. Mayo Clin Proc 1995;70:634-40.
66. Denfield SW, Rosenthal G, Gajarski RJ, et al. Restrictive cardiomyopathies in childhood. Etiologies and natural history. Tex Heart Inst J 1997;24:38-44.
67. Rivenes SM, Kearney DL, Smith EO, et al. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. Circulation 2000;102:876-82.
68. Azakie T, Merklinger SL, McCrindle BW, et al. Evolving strategies and improving outcomes of the modified norwood procedure: a 10-year single-institution experience. Ann Thorac Surg 2001;72:1349-53.
69. Chinnock RE, Bailey LL. Heart transplantation for congenital heart disease in the first year of life. Curr Cardiol Rev 2011;7:72-84.
70. Chrisant MR, Naftel DC, Drummond-Webb J, et al. Fate of infants with hypoplastic left heart syndrome listed for cardiac transplantation: a multicenter study. J Heart Lung Transplant 2005;24:576-82.
71. Guleserian KJ, Armsby LB, Thiagarajan RR, et al. Natural history of pulmonary atresia with intact ventricular septum and right-ventricle-dependent coronary circulation managed by the single-ventricle approach. Ann Thorac Surg 2006;81:2250-7; discussion 2258.
72. Rychik J, Levy H, Gaynor JW, et al. Outcome after operations for pulmonary atresia with intact ventricular

septum. J Thorac Cardiovasc Surg 1998;116:924-31.
73. Ashburn DA, Blackstone EH, Wells WJ, et al. Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. J Thorac Cardiovasc Surg 2004;127:1000-7; discussion 1007-8.
74. Larsen RL, Eguchi JH, Mulla NF, et al. Usefulness of cardiac transplantation in children with visceral heterotaxy (asplenic and polysplenic syndromes and single right-sided spleen with levocardia) and comparison of results with cardiac transplantation in children with dilated cardiomyopathy. Am J Cardiol 2002;89:1275-9.
75. Auerbach SR, Smith JK, Gralla J, et al. Graft survival is better without prior surgery in cardiac transplantation for functionally univentricular hearts. J Heart Lung Transplant 2012;31:987-95.
76. Marino BS. Outcomes after the Fontan procedure. Curr Opin Pediatr 2002;14:620-6.
77. Hess J. Long-term problems after cavopulmonary anastomosis: diagnosis and management. Thorac Cardiovasc Surg 2001;49:98-100.
78. Freedom RM, Hamilton R, Yoo SJ, et al. The Fontan procedure: analysis of cohorts and late complications. Cardiol Young 2000;10:307-31.
79. Rychik J, Goldberg D, Rand E, et al. End-organ consequences of the Fontan operation: liver fibrosis, protein-losing enteropathy and plastic bronchitis. Cardiol Young 2013;23:831-40.
80. Lastinger L, Zaidi AN. The adult with a fontan: a panacea without a cure? Review of long-term complications. Circ J 2013;77:2672-81.
81. Backer CL, Deal BJ, Mavroudis C, et al. Conversion of the failed Fontan circulation. Cardiol Young 2006;16 Suppl 1:85-91.
82. Mavroudis C, Deal BJ, Backer CL. The beneficial effects of total cavopulmonary conversion and arrhythmia surgery for the failed Fontan. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2002;5:12-24.
83. Sheikh AM, Tang AT, Roman K, et al. The failing Fontan circulation: successful conversion of atriopulmonary connections. J Thorac Cardiovasc Surg 2004;128:60-6.
84. Jacobs JP, Quintessenza JA, Chai PJ, et al. Rescue cardiac transplantation for failing staged palliation in patients with hypoplastic left heart syndrome. Cardiol Young 2006;16:556-62.
85. Gossett JG, Almond CS, Kirk R, et al. Outcomes of cardiac transplantation in single-ventricle patients with plastic bronchitis: a multicenter study. J Am Coll Cardiol 2013;61:985-6.
86. Brancaccio G, Carotti A, D'Argenio P, et al. Protein-losing enteropathy after Fontan surgery: resolution after cardiac transplantation. J Heart Lung Transplant 2003;22:484-6.
87. Backer CL, Russell HM, Pahl E, et al. Heart transplantation for the failing Fontan. Ann Thorac Surg 2013;96:1413-9.
88. Bernstein D, Naftel D, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation 2006;114:273-80.
89. Carlo WF, Pearce FB, Kirklin JK. Retransplantation as a successful therapy for post-transplant protein-losing enteropathy. J Heart Lung Transplant 2013;32:472-3.
90. Gossett JG, Canter CE, Zheng J, et al. Decline in rejection in the first year after pediatric cardiac transplantation: a multi-institutional study. J Heart Lung Transplant 2010;29:625-32.
91. Ameduri RK, Zheng J, Schechtman KB, et al. Has late rejection decreased in pediatric heart transplantation in the current era? A multi-institutional study. J Heart Lung Transplant 2012;31:980-6.
92. Chin C, Naftel DC, Singh TP, et al. Risk factors for recurrent rejection in pediatric heart transplantation: a multicenter experience. J Heart Lung Transplant 2004;23:178-85.
93. Webber SA, Naftel DC, Parker J, et al. Late rejection episodes more than 1 year after pediatric heart transplantation: risk factors and outcomes. J Heart Lung Transplant 2003;22:869-75.
94. Pahl E, Naftel DC, Canter CE, et al. Death after rejection with severe hemodynamic compromise in pediatric heart transplant recipients: a multi-institutional study. J Heart Lung Transplant 2001;20:279-87.
95. Everitt MD, Pahl E, Schechtman KB, et al. Rejection with hemodynamic compromise in the current era of pediatric heart transplantation: a multi-institutional study. J Heart Lung Transplant 2011;30:282-8.
96. Ringewald JM, Gidding SS, Crawford SE, et al. Nonadherence is associated with late rejection in pediatric heart transplant recipients. J Pediatr 2001;139:75-8.
97. Boucek MM, Edwards LB, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixth Official Pediatric Report--2003. J Heart Lung Transplant 2003;22:636-52.
98. Kulikowska A, Boslaugh SE, Huddleston CB, et al. Infectious, malignant, and autoimmune complications in pediatric heart transplant recipients. J Pediatr 2008;152:671-7.

99. Schowengerdt KO, Naftel DC, Seib PM, et al. Infection after pediatric heart transplantation: results of a multiinstitutional study. The Pediatric Heart Transplant Study Group. J Heart Lung Transplant 1997;16:1207-16.
100. Gajarski RJ, Smith EO, Denfield SW, et al. Long-term results of triple-drug-based immunosuppression in nonneonatal pediatric heart transplant recipients. Transplantation 1998;65:1470-6.
101. Tran L, Hébert D, Dipchand A, et al. Invasive pneumococcal disease in pediatric organ transplant recipients: a high-risk population. Pediatr Transplant 2005;9:183-6.
102. Stovall SH, Ainley KA, Mason EO Jr, et al. Invasive pneumococcal infections in pediatric cardiac transplant patients. Pediatr Infect Dis J 2001;20:946-50.
103. Lin PL, Michaels MG, Green M, et al. Safety and immunogenicity of the American Academy of Pediatrics--recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. Pediatrics 2005;116:160-7.
104. Gennery AR, Cant AJ, Spickett GP, et al. Effect of immunosuppression after cardiac transplantation in early childhood on antibody response to polysaccharide antigen. Lancet 1998;351:1778-81.
105. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741-51.
106. Rubin RH, Tolkoff-Rubin NE. Infection in the organ transplant patient; the Hegelian dialectic of transplantation. Trans Med Soc Lond 1994-1995;111:81-90.
107. Rubin RH. Prevention and treatment of cytomegalovirus disease in heart transplant patients. J Heart Lung Transplant 2000;19:731-5.
108. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-56.
109. Webber SA, Naftel DC, Fricker FJ, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet 2006;367:233-9.
110. Pandya A, Wasfy S, Hébert D, et al. Varicella-zoster infection in pediatric solid-organ transplant recipients: a hospital-based study in the prevaricella vaccine era. Pediatr Transplant 2001;5:153-9.
111. Zaoutis TE, Webber S, Naftel DC, et al. Invasive fungal infections in pediatric heart transplant recipients: incidence, risk factors, and outcomes. Pediatr Transplant 2011;15:465-9.
112. Ng B, Dipchand A, Naftel D, et al. Outcomes of Pneumocystis jiroveci pneumonia infections in pediatric heart transplant recipients. Pediatr Transplant 2011;15:844-8.
113. Kobayashi D, Du W, L'ecuyer TJ. Predictors of cardiac allograft vasculopathy in pediatric heart transplant recipients. Pediatr Transplant 2013;17:436-40.
114. Costello JM, Wax DF, Binns HJ, et al. A comparison of intravascular ultrasound with coronary angiography for evaluation of transplant coronary disease in pediatric heart transplant recipients. J Heart Lung Transplant 2003;22:44-9.
115. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol 2005;45:1532-7.
116. Kuhn MA, Jutzy KR, Deming DD, et al. The medium-term findings in coronary arteries by intravascular ultrasound in infants and children after heart transplantation. J Am Coll Cardiol 2000;36:250-4.
117. Gudausky TM, Pelech AN, Stendahl G, et al. Dual-axis rotational coronary angiography: a new technique for detecting graft coronary vasculopathy in pediatric heart transplant recipients. Pediatr Cardiol 2013;34:560-5.
118. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003;108:48-53.
119. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003;349:847-58.
120. Pahl E, Crawford SE, Wax DF, et al. Safety and efficacy of pravastatin in pediatric heart transplant recipients. J Heart Lung Transplant 2001;20:230.
121. Kobashigawa JA, Moriguchi JD, Laks H, et al. Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. J Heart Lung Transplant 2005;24:1736-40.
122. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621-7.
123. Chin C, Lukito SS, Shek J, et al. Prevention of pediatric graft coronary artery disease: atorvastatin. Pediatr Transplant 2008;12:442-6.
124. Sachdeva R, Seib PM, Frazier EA, et al. Percutaneous coronary intervention using drug-eluting stents in pediatric heart transplant recipients. Pediatr Transplant 2009;13:1014-9.

125. Chinnock R, Webber SA, Dipchand AI, et al. A 16-year multi-institutional study of the role of age and EBV status on PTLD incidence among pediatric heart transplant recipients. Am J Transplant 2012;12:3061-8.
126. Gajarski RJ, Blume ED, Urschel S, et al. Infection and malignancy after pediatric heart transplantation: the role of induction therapy. J Heart Lung Transplant 2011;30:299-308.
127. Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222-30.
128. Manlhiot C, Pollock-Barziv SM, Holmes C, et al. Post-transplant lymphoproliferative disorder in pediatric heart transplant recipients. J Heart Lung Transplant 2010;29:648-57.
129. Schubert S, Renner C, Hammer M, et al. Relationship of immunosuppression to Epstein-Barr viral load and lymphoproliferative disease in pediatric heart transplant patients. J Heart Lung Transplant 2008;27:100-5.
130. Benkerrou M, Durandy A, Fischer A. Therapy for transplant-related lymphoproliferative diseases. Hematol Oncol Clin North Am 1993;7:467-75.
131. Cacciarelli TV, Green M, Jaffe R, et al. Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. Transplantation 1998;66:1047-52.
132. Newell KA, Alonso EM, Whitington PF, et al. Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. Transplantation 1996;62:370-5.
133. Pescovitz MD. The use of rituximab, anti-CD20 monoclonal antibody, in pediatric transplantation. Pediatr Transplant 2004;8:9-21.
134. Blaes AH, Peterson BA, Bartlett N, et al. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer 2005;104:1661-7.
135. Feingold B, Zheng J, Law YM, et al. Risk factors for late renal dysfunction after pediatric heart transplantation: a multi-institutional study. Pediatr Transplant 2011;15:699-705.
136. Mahle WT, Vincent RN, Kanter KR. Cardiac retransplantation in childhood: analysis of data from the United Network for Organ Sharing. J Thorac Cardiovasc Surg 2005;130:542-6.
137. Chin C, Naftel D, Pahl E, et al. Cardiac re-transplantation in pediatrics: a multi-institutional study. J Heart Lung Transplant 2006;25:1420-4.

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Review Article

Donor selection in heart transplantation

Ahmet Kilic[1], Sitaramesh Emani[2], Chittoor B. Sai-Sudhakar[1], Robert S. D. Higgins[1], Bryan A. Whitson[1]

[1]The Department of Surgery, [2]The Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
Correspondence to: Ahmet Kilic, M.D., Assistant Professor of Surgery. Division of Cardiac Surgery, Department of Surgery, The Ohio State University Wexner Medical Center, 410 W. 10th Avenue, N-816 Doan Hall, Columbus, OH 43210, USA. Email: Ahmet.Kilic@osumc.edu.

Abstract: There is increased scrutiny on the quality in health care with particular emphasis on institutional heart transplant survival outcomes. An important aspect of successful transplantation is appropriate donor selection. We review the current guidelines as well as areas of controversy in the selection of appropriate hearts as donor organs to ensure optimal outcomes. This decision is paramount to the success of a transplant program as well as recipient survival and graft function post-transplant.

Keywords: Heart transplant; donor selection

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Introduction

Despite the rapid growth of ventricular assist devices in heart failure, heart transplantation remains the gold standard for long term outcomes in patients with medically refractory heart failure. The shortcoming in transplantation remains the relatively stable organ supply in the face of rising organ demands. In the United States, the number of heart transplants being performed over the past two decades has remained steady between 2,000 to 2,500 being performed annually. The lack of readily available organs in addition to increased scrutiny over quality and outcomes in health care, has led the Centers for Medicare and Medicaid Services (CMS) to raise the standards for individual institutional outcomes to match national mortality and graft survival outcomes. An important component of outcomes and graft survival is the decision of which organs are suitable as donor organs for transplantation. Appropriate donor selection and management has become paramount in maintaining and optimizing outcomes following heart transplantation.

Donor selection logistics overview

Patients with end stage heart failure who are approved as transplant candidates and listed by the criteria outlined by the United Network for Organ Sharing (UNOS) are eligible for being recipients of an appropriate donor heart (see *Table 1*). In most transplant centers the process is started by the collaboration between the institutional transplant coordinator and the local organ procurement organization. Potential heart donors are identified and a preliminary matching list generated based on UNOS criteria. The primary survey of the donor includes the confirmation of brain death, verification of consent for donation, ABO blood typing, demographics, identification of potential co-morbid conditions (including high risk behavior, substance abuse history, mechanism of death) and the need for cardiopulmonary resuscitation (and if so duration from initiation to return of vital signs). A more heart specific assessment includes the requirement of inotropic support, hemodynamic stability, presence of thoracic trauma, serum cardiac enzyme markers [troponin, or if troponin not available creatinine phosphokinase (CPK)-MB fraction], electrocardiogram, echocardiogram and coronary angiography when indicated (presence of co-morbid conditions and/or age) (1). After a full on-site review of pertinent hospital records, the hemodynamic performance of the heart (including right and left heart catheterization data), visual and manual inspection of the heart, the final acceptance of the heart for transplantation is made by the procuring cardiothoracic surgeon.

Table 1 United Network for Organ Sharing (UNOS) heart allocation algorithm (adapted from http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf#nameddest=Policy_6_Allocation_of_Hearts_a) dated September 1, 2013—accessed January 17, 2014

Status level	Category
Status 1A	Transplant candidate must be admitted to listing transplant center hospital and have at least one of the following devices or therapies in place (I) Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following: (i) left and/or right ventricular assist device implanted candidates may be listed for 30 days under this criterion at any point after being implanted if treating physicians determine they are clinically stable—admittance to hospital not required (ii) total artificial heart (iii) intra-aortic balloon pump; or (iv) extracorporeal membrane oxygenator (ECMO) (II) Mechanical circulatory support with objective medical evidence of significant device-related complications (III) Continuous mechanical ventilation (IV) Continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricular filling pressures
Status 1B	Transplant candidate listed must have at least one of the following devices or therapies in place (I) Left and/or right ventricular assist device implanted; or (II) Continuous infusion of intravenous inotropes
Status 2	A transplant candidate who does not meet the criteria for Status 1A or 1B
Status 7	A transplant candidate who is considered temporarily unsuitable to receive a heart transplant

Table 2 Traditional cardiac donor selection criteria (adapted from Sabiston & Spencer surgery of the chest, 8th ed. Sellke FW, del Nido PJ, Swanson SJ, *et al.* eds. Philadelphia: Saunders Elsevier, 2010)

Traditional cardiac donor selection criteria
Age <55 years old
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Appropriate hemodynamics
Mean arterial pressure >60 mmHg
Central venous pressure 8 to 12 mmHg
Inotropic support less than 10 mg/kg/min (dopamine or dobutamine)
Normal electrocardiogram
Normal echocardiogram
Normal cardiac angiography (if indicated by donor age and history)
Negative serology (hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus)

The two central and unifying concepts in the selection of a donor heart for transplantation are (I) the quality of the donor heart and (II) the matching of the donor heart to the recipient's individual needs. The standard criteria used to accept donor hearts are summarized in *Table 2*. There are institutional as well as individual recipient demand exceptions to these criteria and a certain "art" of balancing recipient need with donor availability. Indeed it may be helpful to think of the matching of the donor heart to the recipient as follows (See *Figure 1*).

Quality assessment of donor heart

The major components for the assessment of the donor

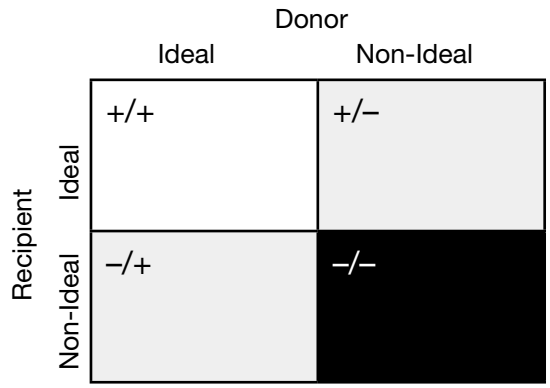

Figure 1 The perfect situation for transplantation would be an ideal donor organ (+) being transplanted into an ideal recipient (+) with minimal co-morbidities and expected great outcomes. In contrast, a marginal donor organ (–) should not be used in recipient with multiple co-morbidities (–).The gray area in transplantation occurs when there is a mismatch between either an ideal donor (+) and non-ideal recipient (–) or vice versa with a non-ideal donor (–) with an ideal, relatively healthy recipient (+). An understanding of the following concepts are mandatory to provide the framework for acceptance of donor hearts and to provide the best organ-recipient matching to provide optimal outcomes.

heart centers around a thorough understanding of the donor history, physical examination, hemodynamic evaluation in addition to laboratory and radiographical (echocardiogram, possible cardiac angiography) findings.

Age

The importance of the age of the donor heart can be traced to early reports on recommendations for heart transplantation. Indeed, an early conservative age for the upper limits of acceptable organs was 35 years of age (2). This has been gradually increased over the past several decades, with most centers now using donor age <55 years as a cut off with the most liberal center using donors up to age 65 and greater. Despite the increase in the upper limits of acceptable age, more than 50% of adult heart donors remain between the ages of 18-34 in the UNOS database with a relatively fixed percentage during the time period of 1988 to 2013.

Multiple studies looking at various recipient and donor factors have shown that age is an independent risk factor for long term mortality. One study looking at the UNOS database with pre-transplant donor and recipient data that broke down the donor age by decades showed an increased odds ratio for mortality based on donor age 50-59 years old: OR 1.8 (1.4-2.0); 40-49 years old: OR 1.7 (1.3-1.7); 30-39 years old: 1.3 (1.1-1.5) all with P<0.05 (3). Other single institutional studies have shown a correlate between early graft failure or patient mortality with the combination of both recipient and donor age >60 (4).

Function of donor heart

It is relatively common for potential donor hearts that have either undergone cardiopulmonary resuscitation, a neurologic insult, thoracic trauma or are on vasoactive/inotropic agents to display non-specific ST changes on electrocardiogram and/or have elevated CPK-MB or troponin levels. Although it has been shown that modestly elevated donor cardiac troponin I levels do not have a negative influence in post-transplant mortality or need for mechanical circulatory support (5), it is important to correlate the findings with echocardiographic examination. In interpretation of the echocardiogram findings; however, it is important to keep in mind the time period between the inciting event, possible myocardial stunning and recovery.

All potential donors should undergo a full echocardiographic examination and it can be argued that this is the single most important tool for examination of donor heart function (6). There should be particular attention paid to the presence of left ventricular hypertrophy (LVH), significant physiologic valvular dysfunction, and depressed ventricular function. A retrospective, single institutional study out of Stanford concentrating on LVH showed decreased survival in heart transplant recipients whose donor heart left ventricular wall thickness exceeded 1.4 mm (7). This underscores the need for a careful echocardiographic examination in any donor with significant age (>40 years old), history of hypertension, substance abuse or risk factors for coronary arterial disease.

Additionally, the need for either inotropic or vasopressor support should be noted. It is important to differentiate between inotropic support secondary to poor cardiac output and vasopressor support secondary to peripheral vasoplegia. Although it is common to need either inotropic or vasopressor support, caution should be used in older donors who may have risk factors for coronary arterial disease, hypertension or left ventricular hypertrophy as stated above. A multi-institutional retrospective study of 512 patients showed that the donor use of norepinephrine infusion did not negatively affect early survival (8). Indeed, an often quoted study out of Papworth Hospital showed an increased donor yield by continuously monitoring

hemodynamic donor data prior to organ procurement. The study consisted of using two sets of hemodynamic data—at initial assessment and just before organ procurement. Donors were subdivided into category A (good function throughout), category B (sub-optimal function then improvement) and category C (decreasing or poor function throughout). Although organs used from categories B and C did not compromise 30 days or 1 year mortality, the authors warned of using these organs in combination with other risk factors (such as older age and longer ischemic times) (9). This underscores the need for initial and continuous evaluation of the potential donor heart during the placement process and how an organized strategy can increase donor usage.

In our institution, we reserve coronary angiography for donor hearts >40 years of age or with significant risk factors (hypertension, diabetes mellitus, hyperlipidemia, family history, smoking or concerning findings on echocardiogram). The presence of coronary arterial disease in the donor heart, as well as increased donor age, been correlated with coronary allograft vasculopathy (10). Although it is our policy not to use donors with multi-vessel coronary arterial disease for transplantation at our institution, several centers have reported with modest success in the use of single- or two-vessel effected donor hearts (11-13).

Decision on appropriateness of heart for recipient

A successful heart transplantation goes beyond just having a perfect donor organ. There are a multitude of other components to the equation including ischemic time, recipient co-morbidities and condition at time of transplantation, size matching, presence of panel reactive antibodies (PRAs) that must all be accounted for to optimize chance of success.

Donor—recipient compatibility

Recently, literature on gender matching of donor to recipient (both without previous sternotomy and with LVADs at bridge to transplant) has shown improved graft survival after transplantation in donor-recipient concordance (14,15). The downside of gender mismatch is observed more in male recipients from female donors and is correlated with both frequency and severity of graft rejection (16). Along those lines, size matching between donor and recipient deserves special mention. The caution of placing a small donor heart size relative to the recipient is warranted; however, size matching based on either body mass index or height may be more precise than weight alone. Extra caution must be exercised not to undersize the donor heart size to the recipient by more than 30% mismatch in patients with known pulmonary hypertension. Additionally, there should be hesitation to oversize by more than 30% mismatch in any recipient who has had a recent large myocardial infarction, LVAD placement or previous sternotomies as the pericardial space may prove to be restrictive.

Ischemic time

Currently, an ischemic time of less than four hours is optimal with some centers showing acceptable outcomes with longer ischemia times (17). There are however, many reports showing that longer ischemia times are associated with higher risk of mortality (3,15,18). In fact, in a study utilizing the UNOS database of over 11,700 patients undergoing heart transplantation, the ischemia time was shown to be an independent risk factor for survival with an OR of 1.7 (1.0-2.8) in patients with an ischemic time >6 hours and an OR of 1.4 (1.3-1.6) in patients with an ischemic time between 4-6 hours ($P<0.05$ for both) (3).

Expanding the donor criteria

The fixed supply of donor hearts with an increasing demand by patients with heart failure, have made the increasing use of available hearts as suitable donor organs a priority. In 2001, a concerted effort to maximize use of organs recovered from the deceased donor was outlined as the Crystal City guidelines (see *Figure 2*) (19). This was in direct response to the mortality of nearly 17% per year while waiting on the transplant list combined with the 42% donor yield based on the UNOS data in 1998. This has indeed born out in other studies as well. In a study looking at 1,872 potential donors in California from 2001-2008, only 45% of organs were used. Among the various reasons listed for not using the available organs were age >50 years, female sex, death from cerebrovascular accident, hypertension, diabetes mellitus, left ventricular dysfunction, wall motion abnormalities and elevated troponin levels. However, the only thing shown on further analysis to increase recipient mortality on the hearts that were used was the presence of diabetes mellitus in the donor organ (20). The presence of insulin dependent donors as an independent risk factor for mortality was also found in the analysis of the UNOS database with an OR of 1.8 (1.0-3.2), $P<0.05$ (21).

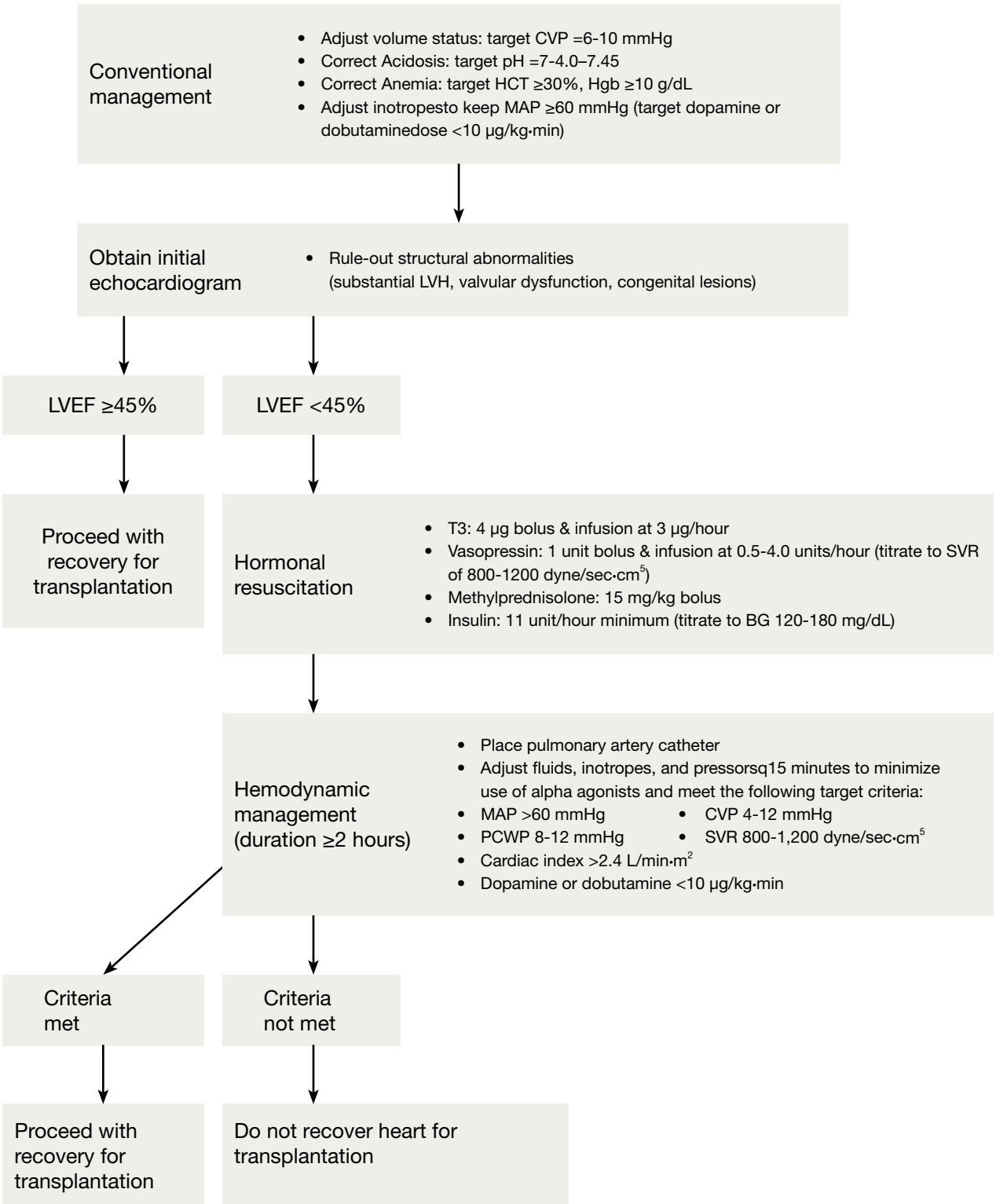

Figure 2 The Crystal City Guidelines for an algorithm for the management of potential heart donors (19). CVP, central venous pressure; HCT, hematocrit; Hgb, hemoglobin; MAP, mean arterial pressure; LVEF, left ventricular ejection fraction; T3, triiodothyronine; SVR, systemic vascular resistance; BG, blood glucose; PCWP, pulmonary capillary wedge pressure.

Additionally, that same study showed that hepatitis C (+) donors had an OR 2.2 (1.1-4.0 CI) for mortality, P<0.05. This has led some to totally abandon the use of high risk social behavior patients (incarceration, unprofessional tattoos, alternative life style practice, active oral or intravenous substance abuse) in heart transplantation and others to be highly selective in their use (22). Interestingly, a recent study of UNOS database showed donor cocaine use did not alter mortality or development of coronary allograft vasculopathy in the first one or five years post-transplantation (23). Some centers have even transplanted recipients with known human immunodeficiency virus (24,25).

A question that has arisen recently is whether or not one can either optimize, repair or recover a potential heart donor to make it suitable for organ transplantation.

Successful use of stress echocardiography to show contractile reserve in donors with low ejection fraction has led to six patients at a single institution being transplanted uneventfully (26). This has previously been demonstrated in a larger, but younger cohort of donors (27). The concept of potential repair of a less than perfect organ is particularly attractive in expanding the donor pool from donation after cardiac death donors. Although there are encouraging reports of no difference in five years mortality and graft survival rates, this has yet to become mainstream (28). Akin to *ex vivo* lung perfusion, donation after cardiac death donors would be a great platform for testing the concept of repair by *ex vivo* heart perfusion (29). An additional benefit would be the ability to perform invasive angiography without the logistical pitfalls of donor transportation from donor institutions that currently lack immediate access to coronary angiography (30).

Special considerations

There is an increasing role of recipient-donor matching in transplantation as it relates to circulating antibodies against human leukocyte antigens and nonhuman leukocyte antigens—or allosensitization. Although there is some dispute as to efficacy of desensitization in post-transplant outcomes, the rise of bridging patients to transplantation with ventricular assist devices and thus exposure to prior allosensitization has thrust this issue to the forefront (31-33). Patients who have allosensitization have a decreased possible donor pool, longer time to transplant and poorer survival (31,34). As a result of this, panel reactive antibodies (PRA) are routinely tested. Traditionally a complement-dependent cytotoxicity assay was used with newer methods of flow cytometry, ELISA and most recently Luminex testing being employed for donor-patient specific crossmatching to ensure optimal transplant outcomes (35). Depending on recipient stability and geographic location, three ways to perform crossmatching are in a prospective, retrospective or virtual manner. Prospective crossmatching involves matching the donor with the recipient by directly testing blood and although ideal, is geographically and logistically challenging (36). Many institutions, including ours, have employed various desensitization protocols to reduce the levels of PRA including intravenous immune globulin, plasmapheresis, rituximab or cyclophosphamide (or a combination) to allow for a bigger donation pool for our recipients (37,38). Some institutions have gone so far as to perform plasmapheresis and alemtuzumab during the cardiopulmonary bypass run in LVAD patients with high PRAs at time of heart transplantation (39). More standard techniques when prospective crossmatching is not available are to either perform the crossmatch in a retrospective or virtual manner. Retrospective crossmatching involves direct comparison of the donor and recipient blood but with the results being available after the donor heart has been used for transplantation. Virtual crossmatch involves comparing the recipients specific PRAs in the past with the donors blood and making decisions based on an indirect comparison. Each of these techniques is appropriate in various clinical scenarios and has decreased the chance of primary graft dysfunction and rejection. Unfortunately, this has come at the price of increased wait list times for recipients with high PRAs.

Some institutions have begun an extended criterion—alternate list for high risk heart transplant recipients. This has allowed the use of marginal donor organs in a recipient cohort that is sicker and without much alternatives or physiologic reserve (40,41). In a study from Duke University, patients transplanted from the alternative list were compared to patients with ventricular assist device as destination therapy. Although survival rates were similar after one year (82% for transplanted group *vs.* 78% for LVAD group), the transplanted group had a trend towards, but not statistically significant, better three years survival (64% versus 50%, P=0.33) (34).

Conclusions

In this current era of transplantation, there is increased focus on outcomes as it relates to volume and quality (42). Although we are well aware that institutional volume is not

a surrogate for center quality, we must resist the temptation to be risk-averse and deny patients the chance at receiving lifesaving organs (43). In order to best accomplish this, it is imperative to have a better understanding of donor risk factors that can affect graft and patient survival (3,44,45). The continued increase in LVAD usage combined with the discrepancy between donor organ supply and demand means getting the most out of the organs that are used. Additionally, there should be a concerted effort between organ procurement organizations, transplant programs and donor hospitals to maximize the utilization of marginal donor hearts.

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References

1. John R. Donor management and selection for heart transplantation. Semin Thorac Cardiovasc Surg 2004;16:364-9.
2. Griepp RB, Stinson EB, Clark DA, et al. The cardiac donor. Surg Gynecol Obstet 1971;133:792-8.
3. Hong KN, Iribarne A, Worku B, et al. Who is the high-risk recipient? Predicting mortality after heart transplant using pretransplant donor and recipient risk factors. Ann Thorac Surg 2011;92:520-7; discussion 527.
4. Cannata A, Botta L, Colombo T, et al. Does the cardioplegic solution have an effect on early outcomes following heart transplantation? Eur J Cardiothorac Surg 2012;41:e48-52; discussion e52-3.
5. Khush KK, Menza RL, Babcock WD, et al. Donor cardiac troponin I levels do not predict recipient survival after cardiac transplantation. J Heart Lung Transplant 2007;26:1048-53.
6. Hashimoto S, Kato TS, Komamura K, et al. Utility of echocardiographic evaluation of donor hearts upon the organ procurement for heart transplantation. J Cardiol 2011;57:215-22.
7. Kuppahally SS, Valantine HA, Weisshaar D, et al. Outcome in cardiac recipients of donor hearts with increased left ventricular wall thickness. Am J Transplant 2007;7:2388-95.
8. Fiorelli AI, Branco JN, Dinkhuysen JJ, et al. Risk factor analysis of late survival after heart transplantation according to donor profile: a multi-institutional retrospective study of 512 transplants. Transplant Proc 2012;44:2469-72.
9. Stoica SC, Satchithananda DK, Charman S, et al. Swan-Ganz catheter assessment of donor hearts: outcome of organs with borderline hemodynamics. J Heart Lung Transplant 2002;21:615-22.
10. Gao HZ, Hunt SA, Alderman EL, et al. Relation of donor age and preexisting coronary artery disease on angiography and intracoronary ultrasound to later development of accelerated allograft coronary artery disease. J Am Coll Cardiol 1997;29:623-9.
11. Pinto CS, Prieto D, Antunes MJ. Coronary artery bypass graft surgery during heart transplantation. Interact Cardiovasc Thorac Surg 2013;16:224-5.
12. Grauhan O, Siniawski H, Dandel M, et al. Coronary atherosclerosis of the donor heart--impact on early graft failure. Eur J Cardiothorac Surg 2007;32:634-8.
13. Marelli D, Laks H, Bresson S, et al. Results after transplantation using donor hearts with preexisting coronary artery disease. J Thorac Cardiovasc Surg 2003;126:821-5.
14. Maltais S, Jaik NP, Feurer ID, et al. Mechanical circulatory support and heart transplantation: donor and recipient factors influencing graft survival. Ann Thorac Surg 2013;96:1252-8.
15. Kilic A, Weiss ES, Allen JG, et al. Simple score to assess the risk of rejection after orthotopic heart transplantation. Circulation 2012;125:3013-21.
16. Welp H, Spieker T, Erren M, et al. Sex mismatch in heart transplantation is associated with increased number of severe rejection episodes and shorter long-term survival. Transplant Proc 2009;41:2579-84.
17. Morgan JA, John R, Weinberg AD, et al. Prolonged donor ischemic time does not adversely affect long-term survival in adult patients undergoing cardiac transplantation. J Thorac Cardiovasc Surg 2003;126:1624-33.
18. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:549-62.
19. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. Circulation 2002;106:836-41.
20. Khush KK, Menza R, Nguyen J, et al. Donor predictors of allograft use and recipient outcomes after heart transplantation. Circ Heart Fail 2013;6:300-9.
21. Hong KN, Iribarne A, Worku B, et al. Who is the high-

risk recipient? Predicting mortality after heart transplant using pretransplant donor and recipient risk factors. Ann Thorac Surg 2011;92:520-7; discussion 527.
22. Xu DS, Hartman D, Ludrosky K, et al. Impact of donor high-risk social behaviors on recipient survival in cardiac transplantation. Transplantation 2010;89:873-8.
23. Brieke A, Krishnamani R, Rocha MJ, et al. Influence of donor cocaine use on outcome after cardiac transplantation: analysis of the United Network for Organ Sharing Thoracic Registry. J Heart Lung Transplant 2008;27:1350-2.
24. Sims DB, Uriel N, González-Costello J, et al. Human immunodeficiency virus infection and left ventricular assist devices: a case series. J Heart Lung Transplant 2011;30:1060-4.
25. Krishan K, Pinney S, Anyanwu AC. Successful left ventricular assist device bridge to transplantation in a patient with end-stage heart failure and human immunodeficiency virus. Artif Organs 2012;36:759.
26. Bombardini T, Gherardi S, Leone O, et al. Transplant of stunned donor hearts rescued by pharmacological stress echocardiography: a "proof of concept" report. Cardiovasc Ultrasound 2013;11:27.
27. Kono T, Nishina T, Morita H, et al. Usefulness of low-dose dobutamine stress echocardiography for evaluating reversibility of brain death-induced myocardial dysfunction. Am J Cardiol 1999;84:578-82.
28. Quader MA, Wolfe LG, Kasirajan V. Heart transplantation outcomes from cardiac arrest-resuscitated donors. J Heart Lung Transplant 2013;32:1090-5.
29. White CW, Ali A, Hasanally D, et al. A cardioprotective preservation strategy employing ex vivo heart perfusion facilitates successful transplant of donor hearts after cardiocirculatory death. J Heart Lung Transplant 2013;32:734-43.
30. Ghodsizad A, Bordel V, Ungerer M, et al. Ex vivo coronary angiography of a donor heart in the organ care system. Heart Surg Forum 2012;15:E161-3.
31. Al-Mohaissen MA, Virani SA. Allosensitization in heart transplantation: an overview. Can J Cardiol 2014;30:161-72.
32. Shankar N, Daly R, Geske J, et al. LVAD implant as a bridge to heart transplantation is associated with allosensitization as measured by single antigen bead assay. Transplantation 2013;96:324-30.
33. Kilic A, Ailawadi G. Left ventricular assist devices in heart failure. Expert Rev Cardiovasc Ther 2012;10:649-56.
34. Wright EJ, Fiser WP, Edens RE, et al. Cardiac transplant outcomes in pediatric patients with pre-formed anti-human leukocyte antigen antibodies and/or positive retrospective crossmatch. J Heart Lung Transplant 2007;26:1163-9.
35. Chaidaroglou A, Skoura A, Degiannis D. Comparative performance evaluation of a donor-specific bead-based crossmatch technique for the detection of donor-specific anti-HLA antibodies in heart transplantation. Transplant Proc 2013;45:2005-8.
36. Patel JK, Kobashigawa JA. Improving survival during heart transplantation: diagnosis of antibody-mediated rejection and techniques for the prevention of graft injury. Future Cardiol 2012;8:623-35.
37. Ballew CC, Bergin JD. Management of patients with preformed reactive antibodies who are awaiting cardiac transplantation. Am J Crit Care 2005;14:46-51.
38. Chih S, Tinckam KJ, Ross HJ. A survey of current practice for antibody-mediated rejection in heart transplantation. Am J Transplant 2013;13:1069-74.
39. Lick SD, Beckles DL, Piovesana G, et al. Transplantation of high panel-reactive antibody left ventricular assist device patients without crossmatch using on-bypass pheresis and alemtuzumab. Ann Thorac Surg 2011;92:1428-34.
40. Laks H, Marelli D. The alternate recipient list for heart transplantation: a model for expansion of the donor pool. Adv Card Surg 1999;11:233-44.
41. Daneshmand MA, Rajagopal K, Lima B, et al. Left ventricular assist device destination therapy versus extended criteria cardiac transplant. Ann Thorac Surg 2010;89:1205-9; discussion 1210.
42. Abecassis MM, Burke R, Klintmalm GB, et al. American Society of Transplant Surgeons transplant center outcomes requirements--a threat to innovation. Am J Transplant 2009;9:1279-86.
43. Kilic A, Weiss ES, Yuh DD, et al. Institutional factors beyond procedural volume significantly impact center variability in outcomes after orthotopic heart transplantation. Ann Surg 2012;256:616-23.
44. Weiss ES, Allen JG, Kilic A, et al. Development of a quantitative donor risk index to predict short-term mortality in orthotopic heart transplantation. J Heart Lung Transplant 2012;31:266-73.
45. Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). Ann Thorac Surg 2011;92:914-21; discussion 921-2.

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Surgical Technique

Heart transplantation

Allen Cheng, Mark S. Slaughter

Department of Cardiovascular and Thoracic Surgery, University of Louisville, Louisville, Kentucky 40202, USA

Correspondence to: Mark S. Slaughter, M.D. Chair, Department of Cardiovascular and Thoracic Surgery, University of Louisville, 201 Abraham Flexner Way, Suite 1200, Louisville, KY 40202, USA. Email: mark.slaughter@louisville.edu.

Abstract: Heart failure remains a major global problem with approximately 6 million individuals suffering from heart failure in the United States alone. The surgical technique of heart transplantation, popularized by Dr. Norman Shumway, has led to its success and currently remains the best treatment options for patients with end-stage. However, with the continued limitation of donor organs and the rapid development of ventricular assist device technology, the number of patients bridged to transplant with mechanical circulatory support has increased significantly. This has created some new technical challenges for heart transplantation. Therefore, it is now important to be familiar with multiple new technical challenges associated with the surgical techniques of heart transplantation with an ultimate goal in reducing donor heart ischemic time, recipient cardiopulmonary bypass time and post-operative complications. In this review, we described our technique of heart transplantation including the timing of the operation, recipient cardiectomy and donor heart implantation.

Keywords: Heart transplantation

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Introduction

Heart transplantation remains the gold standard therapy for end-stage congestive heart failure despite the continued development of the new treatments including biventricular pacing, stem cell therapies and mechanical circulatory support. Dr. Shumway paved the way for the widespread clinical acceptance of cardiac transplantation starting with his experimental work in the laboratory dating back to the 1950s. Beginning with his early work including topical hypothermia and bi-atrial anastomosis (1-3), the surgical technique and medical management of heart transplantation has continued to evolve and with the improved success has resulted in over 5,000 heart transplantations worldwide per year. At our center, we prefer the bicaval orthotopic heart transplant technique. The bicaval approach preserves normal atrial morphology, sinus node and valvular function. Previous studies have shown the bicaval technique was associated with reduced hospital stay, decreased incidence of atrial dysrhythmias and conduction disturbances, less mitral and tricuspid incompetence secondary to atrioventricular geometry distortion and right ventricular failure (4-6). With the increased and successful use of left ventricular assist devices (LVADs), as a bridge-to-transplant, it has dramatically influenced not only the number of patients receiving heart transplant with a LVAD but it has also increased the technical challenges in heart transplantation. This new challenge of LVAD removal/explant, prior to proceeding with the donor heart implantation, has added new challenges not only technically but frequently with the timing of the operation and the sequence of the anastomoses. The ultimate goal is to limit donor heart ischemic time, recipient cardiopulmonary bypass time, post-operative complications and maintain the overall success that heart transplantation has achieved over the years. In this chapter, we review our technique in heart transplantation including the timing of the operation, recipient cardiectomy and donor heart implantation.

Technique

Timing of the operation

The timing of donor and recipient cardiectomy is critical

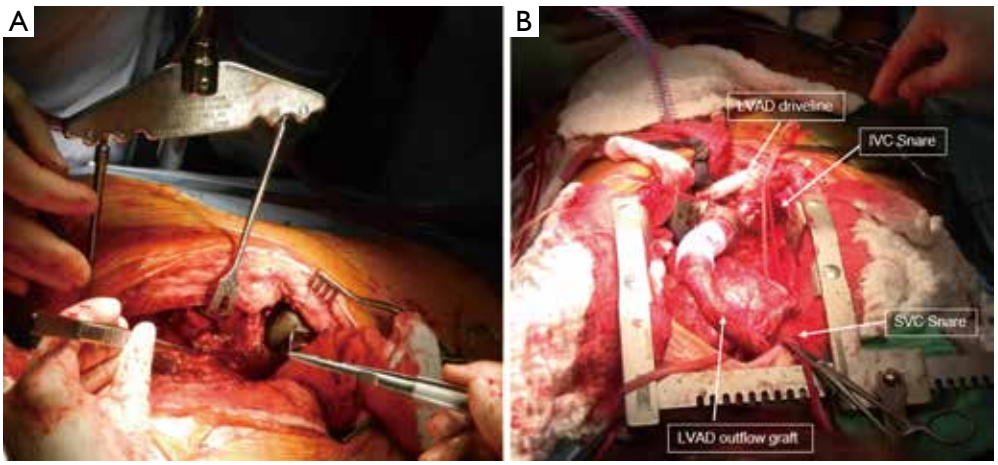

Figure 1 (A) A redo-sternotomy in a patient with previous LVAD placement. Rult retractor (Rultract, Cleveland, OH) was used to assist in exposure for the dissection of the left ventricular apex and LVAD. (B) Completion of the dissection with LVAD outflow graft and LVAD driveline exposed. Snares were placed around the SVC and IVC. LVAD, left ventricular assist device; SVC, superior vena cava; IVC, inferior vena caca.

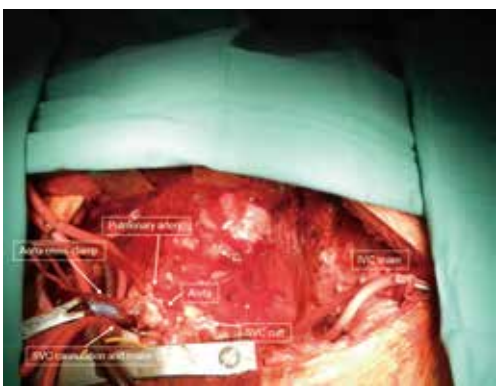

Figure 2 Completion of the recipient cardiectomy with aorta cross-clamped and vena cavae snared. IVC cannulation was done via the right common femoral vein. SVC, superior vena cava; IVC, inferior vena caca.

in minimizing the allograft ischemic time and recipient cardiopulmonary bypass time. The donor ischemic time should be less than 6 hours but more preferably and routinely less than 4 hours. Frequent communication between the procurement and implanting teams is necessary and will allow optimal coordination of the procedures. The recipient operation should be started sufficiently in advance of the arrival of the donor heart to minimize ischemic time. We usually allow at least 1 hour from skin incision to the arrival of the donor's heart for recipients who have not undergone a previous sternotomy. In patient with prior sternotomy or LVAD placement, this period is extended to 2 hours to allow adequate time to complete the dissection of the recipient's heart. Factors that have to be considered when coordinating timing of the operations include: time the abdominal organ procurement teams need to complete their dissection before cross-clamping; organ transportation time, time required for the anesthesia team for induction and monitoring lines placement in the recipient, and time required for recipient heart dissection and explantation, especially in patient with LVAD and prior sternotomies. The perfect coordination of the donor and recipient operations is one of the key components in the attempt to reduce donor heart ischemic time and recipient cardiopulmonary bypass time.

Recipient cardiectomy

Median sternotomy is performed and pericardial cradle is created. The aorta, pulmonary artery, superior vena cava (SVC) and inferior vena caca (IVC) are dissected and isolated away from their adjacent structures. Umbilical tape snares are passed around the SVC and IVC (*Figure 1*). After heparinization, the distal ascending aorta (just proximal to the innominate artery), SVC and ICV are cannulated for cardiopulmonary bypass. In redo sternotomy, enough native heart is dissected so that at the minimal the SVC, IVC and the ascending aorta are accessible for cannulation and establishing cardiopulmonary bypass. If needed, the remainder of the dissection can then be completed once on cardiopulmonary bypass. In patients with a previous sternotomy, the femoral vein can be percutaneously cannulated for IVC drainage (*Figure 2*) which will also allow more room for the IVC anastomosis during heart

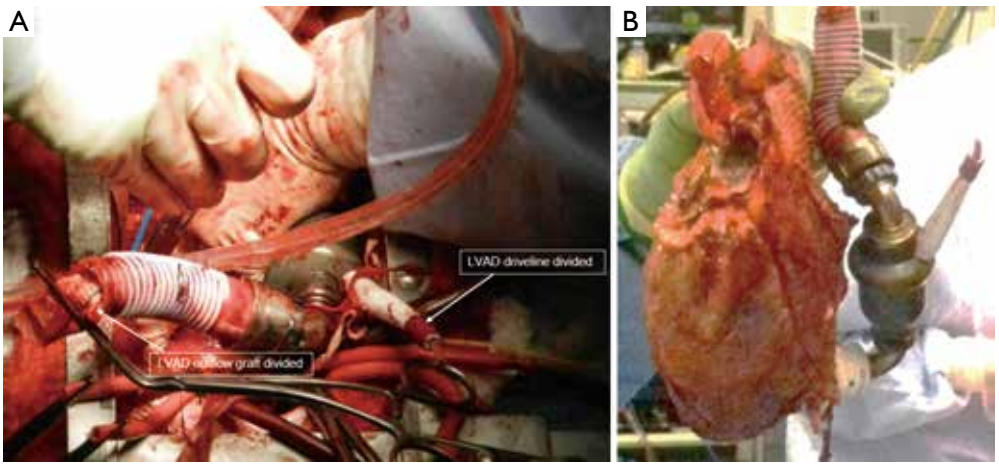

Figure 3 (A) LVAD driveline was divided and outflow graft was clamped and divided; (B) Recipient heart was resected along with the LVAD. LVAD, left ventricular assist device.

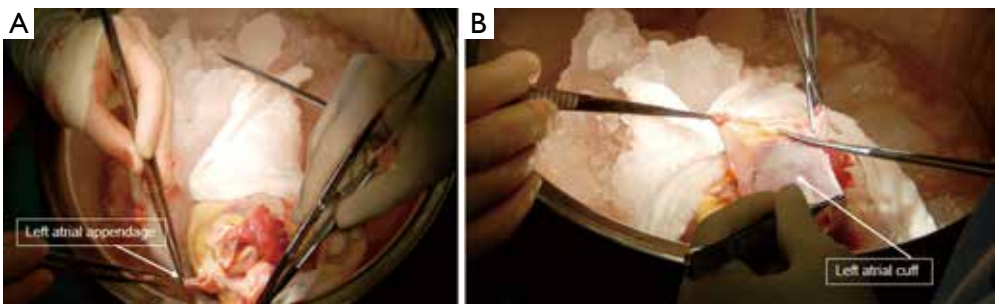

Figure 4 Back table donor heart preparation. The left atrial appendage incision was closed and the left atrial cuff was created. The donor heart was examined for patent ductus ovale, valvular abnormality and congenital anomaly.

implantation. After cardiopulmonary bypass is initiated, the recipient aorta is cross-clamped and the snares around the SVC and IVC are tightened. For patients with a LVAD, the LVAD outflow graft should be clamped and the device should be turned off before the initiation of cardiopulmonary bypass (*Figure 3*). The aorta and pulmonary artery are divided just above the semilunar valves. The right atrium is excised completely by transecting the SVC and then the IVC near its their junction with the main body of the right atrium. On opening the SVC, the swan ganz catheter should be removed and preserved. Any pacing leads are placed on tension and then divided. The heart is retracted inferiorly to expose the left atrial dome. The left atrial dome is opened and the incision is extended towards the mitral valve annulus in a circumferential fashion. At this point, the native heart can be removed. After removing the native heart, the left atrial appendage can be removed and the left atrial cuff trimmed. The aorta, pulmonary artery, IVC and SVC are usually individually trimmed to appropriate lengths after the donor heart has been inspected and the left atrial anastomosis completed cuff. For patients with a LVAD, we remove the LVAD with the native heart. The driveline is dissected, mobilized and divided from within the chest cavity (*Figure 3*). The driveline exit site is contaminated, and hence the remaining driveline should be removed at the end of the procedure after the recipient chest is closed.

At this point, the donor heart is removed from the procurement container and is the start of the "warm ischemic" time. The donor heart is examined on the back table for a patent foreman ovale, valve defects or congenital anomaly. If the lungs were not procured, the left atrial cuff is then created by connecting the orifices of the pulmonary veins. The left atrial appendage incision should be closed if it was used for venting during the procurement (*Figure 4*).

Implantation of the donor heart

At our center, the bicaval technique is the preferred approach.

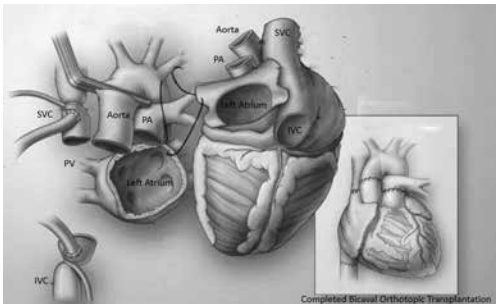

Figure 5 An illustration of the recipient mediastinum and the donor heart with the first stitch at the level of the donor left atrial appendage and recipient left superior pulmonary vein. The illustration on the right showed the completion of a bicaval orthotopic heart transplantation. PA, pulmonary artery; PV, pulmonary vein; SVC, superior vena cava; IVC, inferior vena caca.

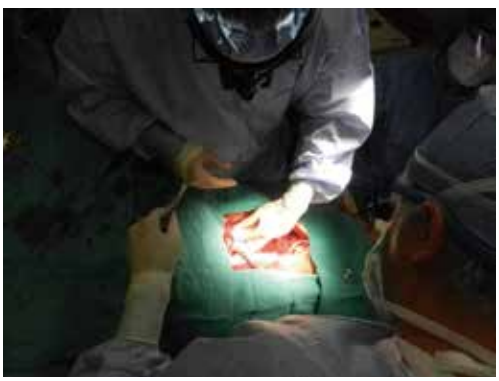

Figure 6 The donor heart was placed into the recipient left chest after 3-4 stiches was placed in the left atrial cuff at the level of the left superior pulmonary vein (recipient) and left atrial appendage (donor).

Figure 7 The aorta anastomosis. Aortic cross-clamp was removed after the aorta anastomosis.

We perform our anastomoses in the following order: left atrium, pulmonary artery, aorta, IVC and SVC. If necessary, the aortic cross-clamp can be removed immediately after the left atrial and aortic anastomosis in order to allow earlier allograft re-perfusion. However, more commonly, we remove the aortic cross-clamp after completing the left atrial, pulmonary artery, aortic and SVC anastomoses.

The anastomosis of the donor and recipient left atrium is performed first with a long double-armed running 3-0 polypropylene suture. The first stitch is placed across the recipient atrial cuff at the level of the left superior pulmonary vein and then to the donor atrial cuff at the base of the left atrial appendage (*Figure 5*). After 3-4 stitches sewing towards the left inferior pulmonary vein, the donor heart is then parachuted down into the recipients' chest (*Figure 6*). The donor heart is wrapping in a sponge with slushed ice for cooling and to insulate it from direct warming from the adjacent thoracic structures. Stay stitches can be placed at the septum at the level of the right superior pulmonary vein and right inferior pulmonary vein for retraction and exposure. The suture line is continued around the superior and inferior borders of the left atrium and then tied. It is important to continually assess size discrepancy between donor and recipient atria so that appropriate plication of excess tissue may be performed. The surgeon should also be sensitive to the respective positions of the recipient and donor IVC and SVC while constructing the left atrial suture line. A left ventricular vent should be placed through the right superior pulmonary vein for de-airing and to avoid accumulation of venous return from the lungs, which can lead to warming of the donor heart during implantation. The pulmonary arteries are trimmed and tailored to the appropriate length and the anastomosis starts on the back wall of the artery with a double-armed 4-0 polypropylene suture. It is crucial that the pulmonary artery ends be trimmed to eliminate any redundancy in the vessel that might cause kinking. The suture line is continued on the front wall and the sutures are tied at the anteromedial aspect of the pulmonary artery. The anastomosis of the aorta is then performed in the same manner with a double-armed 4-0 polypropylene suture in a running fashion (*Figures 5*,7). It should be noted that, unlike the pulmonary artery, some redundancy in length is desired because it can allow better visualization of the posterior aortic suture line when necessary. With the patient in the trendelenburg position, a dose of steroids are administered and the aortic cross-clamp is removed. The SVC and IVC anastomoses are performed on a beating heart. Intravenous methylprednisolone (500 mg)

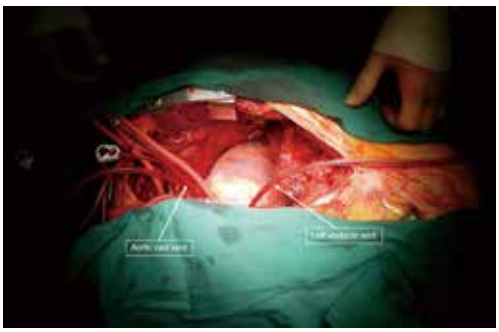

Figure 8 Completion of the allograft implantation. Aortic root and left ventricular vent were used for de-airing.

is administered before the removal of the aortic cross-clamp. An aortic root vent can be placed into the ascending aorta for de-airing (*Figure 8*). The IVC anastomosis is performed with a double-armed 4-0 polypropylene suture in an end-to-end fashion starting with the posterior wall. The SVC anastomosis is performed in the same fashion. The length of the SVC should be tailored to avoid extra length and possible kinking (*Figure 5*). Before the weaning from cardiopulmonary bypass, sufficient time is needed to allow adequate reperfusion. Roughly, approximately 15 minutes reperfusion for each hour of ischemic time, the patient is gradually weaned from cardiopulmonary bypass. Preexisting pulmonary hypertension and the effects of cardiopulmonary bypass on pulmonary vascular resistance may give rise to perioperative right ventricular dysfunction following heart transplantation. We routinely use inhaled flolan or nitric oxide as an adjunct to lower pulmonary vascular resistance before coming off cardiopulmonary bypass and to help prevent right heart failure. Pulmonary artery venting can also be used to assist in the weaning of cardiopulmonary bypass and to avoid acute dilation of the right ventricle. It is also important to keep the pCO_2 between 30-35 torr with minute ventilation adjustment to maximize pulmonary vasodilation. The heart rate of the newly implanted heart should be maintained between 100-120 beats per minutes with isoproterenol or pacing wires to allow adequate cardiac output from both the left and right ventricles. Intraoperative transesophageal echocardiogram is utilized to inspect all valves , anastomotic orientation and right and left ventricular function.

Conclusions

The advancement in the surgical technique of heart transplantation has contributed to its success and it remains the gold standard therapy for end-stage congestive heart failure with demonstrated improvement in patient survival and quality of life. Our technique of heart transplantation has evolved over time and specific modifications for including the explant of a LVAD now included with the primary goals of reduction in allograft ischemic time, recipient cardiopulmonary bypass time and post-operative complications. With the persistent limitation of suitable donor hearts, continued future developments will be needed in the areas of donor allocation, use of "marginal" donor hearts and the technological advancement in mechanical circulatory assist devices.

Acknowledgements

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References

1. Lower RR, Stofer RC, Shumway NE. Homovital transplantation of the heart. J Thorac Cardiovasc Surg 1961;41:196-204.
2. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum 1960;11:18-9.
3. Lower RR, Dong E Jr, Shumway NE. Long-term survival of cardiac homografts. Surgery 1965;58:110-9.
4. Weiss ES, Nwakanma LU, Russell SB, et al. Outcomes in bicaval versus biatrial techniques in heart transplantation: an analysis of the UNOS database. J Heart Lung Transplant 2008;27:178-83.
5. Milano CA, Shah AS, Van Trigt P, et al. Evaluation of early postoperative results after bicaval versus standard cardiac transplantation and review of the literature. Am Heart J 2000;140:717-21.
6. Aziz T, Burgess M, Khafagy R, et al. Bicaval and standard techniques in orthotopic heart transplantation: medium-term experience in cardiac performance and survival. J Thorac Cardiovasc Surg 1999;118:115-22.

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Review Article

Left ventricular assist devices as a bridge to cardiac transplantation

Christopher T. Holley, Laura Harvey, Ranjit John

University of Minnesota Department of Surgery, Minneapolis, MN 55455, USA

Correspondence to: Ranjit John, MD. Associate Professor, Division of Cardiovascular and Thoracic Surgery, University of Minnesota, Minneapolis, MN 55455, USA. Email: johnx008@umn.edu.

Abstract: Heart failure remains a significant cause of morbidity and mortality, affecting over five million patients in the United States. Continuous-flow left ventricular assist devices (LVAD) have become the standard of care for patients with end stage heart failure. This review highlights the current state of LVAD as a bridge to transplant (BTT) in patients requiring mechanical circulatory support (MCS).

Keywords: Left ventricular assist devices (LVAD); bridge to transplant (BTT); mechanical circulatory support (MCS)

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Introduction

Despite advances in medical technology and renewed interest in preventative health care, heart failure remains a significant cause of morbidity and mortality in the United States. Partially because of the improvements in the treatment of heart failure, more patients are living with advanced stage heart failure than ever before. By 2010, over five million Americans carried a diagnosis of heart failure with another 825,000 patients receiving the diagnosis in that year alone (1). The standard of care for end stage heart failure patients remains cardiac transplantation in patients deemed to be appropriate candidates. However, the disparity between available donor hearts and recipients waiting on the cardiac transplant list has continued to grow. With the advent of durable and reliable mechanical circulatory support (MCS), bridge to transplant (BTT) therapy has become the standard of care for many patients awaiting transplant who develop end-stage organ dysfunction or a life threatening exacerbation of their existing heart failure (2-4).

Background

Early efforts at MCS focused on short term, extra corporeal assist devices. As technology improved throughout the 1990s, durable and implantable assist devices were introduced that revolutionized the surgical treatment of heart failure refractory to medical intervention. While cardiac transplantation remains the gold standard, the availability of viable options for long-term mechanical support in patients with advanced stage heart failure ushered in the current era of MCS as a bridge to cardiac transplantation.

Initially conceived as an alternative to cardiac transplantation, the benefit and viability of left ventricular assist devices (LVAD) as a BTT was demonstrated in the landmark study conducted by Frazier *et al.* in 1995. In this nonrandomized study comparing implantation of an early model pulsatile LVAD versus optimal medical therapy, a 55% reduction in pre-transplant mortality was seen with LVAD support and a significant improvement in 1 year post-transplant survival in patients supported with a pulsatile LVAD (2). In addition, the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated that LVAD implantation improved survival compared to optimal medical management in patients ineligible for heart transplantation (5).

Despite promising results, the early implantable mechanical circulatory devices, which were of the pulsatile, volume displacement variety, did not have the durability required to provide ongoing, long-term support without frequent LVAD pump exchanges (5). An unacceptably high rate of device infection or malfunction requiring LVAD exchange [up to 65% by 2 years of support by one study (6)] limited widespread acceptance and use of this first generation, pulsatile LVADs. In addition, they were large,

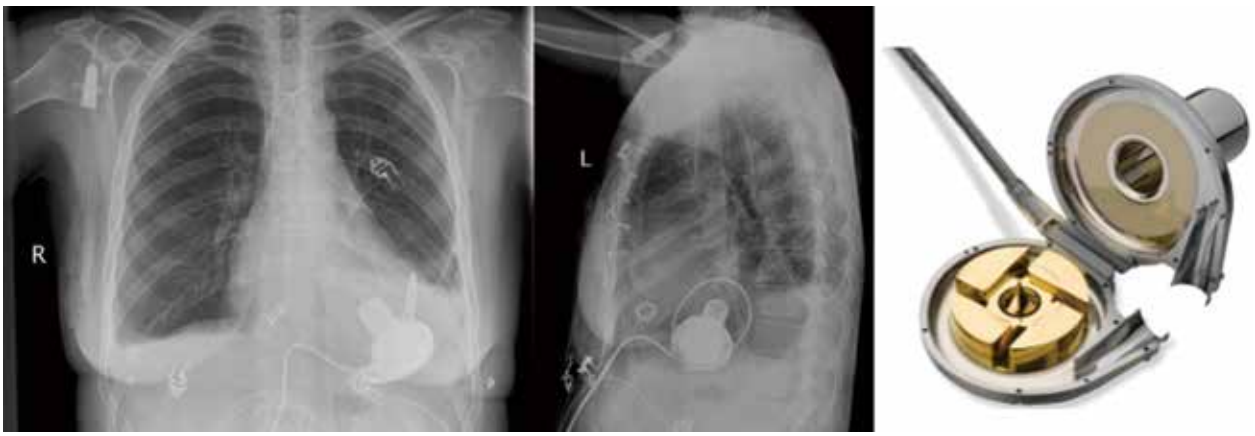

Figure 1 Heartware VAD (HVAD).

Figure 2 Heartmate II [reprinted from (7)].

limiting their use in women, adolescents, and some men. The development of second generation continuous flow (CF), rotary pump devices [Heartware VAD (HVAD) (*Figure 1*), Heartmate II (*Figure 2*)] that were smaller, quieter, and more durable allowed for longer durations of support and the ability to implant LVADs in underserved patient populations.

In the current era, with continued improvements in LVAD technology, improved patient selection, and post-operative clinical optimization, patients implanted with ventricular assist devices are designated as BTT, meant to act as a mechanical assist in the ambulatory setting as a bridge to cardiac transplantation, or destination therapy (DT), meant as a permanent solution for patients not deemed to be transplant candidates. While the BTT and DT designations allow for the categorizing of patients, helping standardize patient populations for outcomes based studies, in reality patients may crossover from one group to the other as their clinical condition deteriorates or improves, or other medical co-morbidites cause a once transplant-eligible patient to remain on indefinite MCS. In fact, the term "bridge to decision" has become common at many institutions, wherein a patient is implanted with an LVAD and the decision to for eventual cardiac transplantation UNOS listing is determined by their clinical course in the months following implantation. In addition, as devices have improved and experience with MCS become more extensive, a subset of patients have been found to recover myocardial function after temporary LVAD support (8), eventually allowing for explanation of the LVAD, leading these patients to be referred to as "bridge to recovery". In the end, it is important to recognize that a patient's initial designation as BTT or DT is not a diagnosis but part of an ongoing clinical assessment of the patient's functional status and response to LVAD therapy.

Patient selection

Patient selection is critical for optimal outcomes after LVAD implantation. Patients being considered for MCS must first have all modifiable or reversible causes of heart failure optimally treated medically prior to surgical consideration of LVAD implantation. Additionally, their transplant eligibility

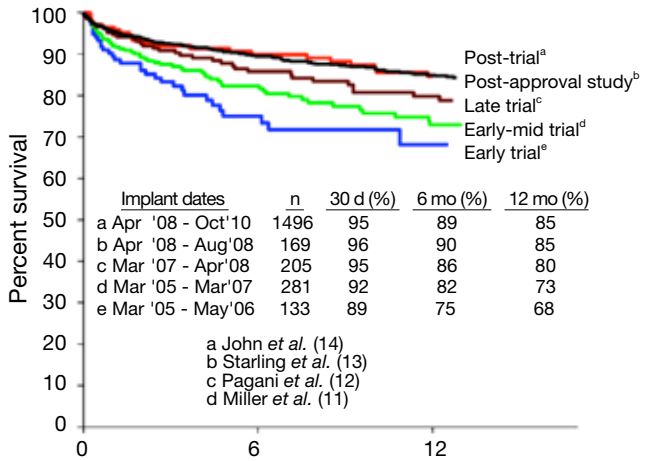

Figure 3 Heartmate II survivals by era (11-14).

should be assessed to determine type and timing of LVAD implantation. Generally, patients with a high one-year mortality from heart failure, those who are inotrope dependent, or those who are otherwise unable to maintain end-organ function and are not expected to recover without long term MCS should be considered for LVAD placement (9). New York Heart Association functional class should be assessed and Interagency Registry for Mechanical Assisted Support (INTERMACS) profiles should be determined. Additionally, cognitive and psychosocial testing, as well as family/community support networks must be considered when determining patient eligibility for LVAD implantation. In general, patients with irreversible multi-organ dysfunction are not eligible for LVAD implantation.

Currently, optimal timing for implantation of an LVAD remains unclear. However, many centers believe that in transplant eligible patients' early implantation, prior to the development of end organ dysfunction and inotrope dependence, improves outcomes, quality of life, and survival to transplant. Pre-operative risk assessment scores remain imperfect but have highlighted risk factors, such as pre-existing renal dysfunction, liver dysfunction, poor nutritional status, and coagulopathy, which have adverse effects on patient outcomes post-VAD implantation (10), helping to identify patients who may not benefit from an LVAD.

Contemporary results

Device selection and outcomes

Outcomes in patients supported by LVADs have continued to consistently improve over time with improvement in device design, patient selection, and post-operative care.

CF-LVADs appear to have excellent outcomes when used as a BTT (11) as measured by survival to transplant, cardiac recovery, or ongoing LVAD support at six months. In the contemporary era, improvements in LVAD technology and durability have led to an increasing use of LVAD as a BTT with alternative therapeutic options becoming increasingly obsolete. Supporting patients with intravenous inotropes in order to delay LVAD implantation is becoming increasingly rare. Improvements in survival, device durability, and reduced adverse events have led many centers to eliminate inotropic therapy as an alternative to LVADs.

Following the US Food and Drug Administration's (FDA) approval of the Thoratec Heartmate II CF-LVAD as a BTT in 2008, improvements in survival have continued to increase. One year survival from the initial 133 patients reported by Miller *et al.* in 2007 was 68% (11). By 2009, this number had climbed to 73% one year survival (12), and by 2011, the one year survival reported by INTERMACS from the postapproval study had climbed to 85% (13) (see *Figure 3*). Most importantly, patients with CF-LVADs were noted to have improved survival compared with patients supported by pulsatile flow devices (15).

Another CF-LVAD that has demonstrated similar outcomes and improvements in quality of life metrics is the Heartware Ventricular Assist System. HVAD, which utilizes centrifugal flow technology rather than the axial flow design seen in the Heartmate II, is designed with an integrated inflow cannula meant to allow for complete intra-pericardial implantation. The HVAD has consistently demonstrated excellent survival outcomes (16,17), with the ADVANCE trial reporting 86% survival at one year post-implant with a significant improvement in functional capacity and quality of life (17). Compared with optimal medical therapy, the improvements seen in 6-minute walk times was nearly three times better for patients implanted with the HVAD (17,18), further highlighting the dramatic improvements that can be seen with CF-LVAD implantation in heart failure patients.

The Jarvik 2000 is yet another example of a second generation, CF LVAD which utilizes axial flow, but is unique in that it uses a single, vanned impeller and its pump is positioned intraventricularly with the outflow graft most commonly anastomosed to the descending aorta, rather than the ascending aortic outflow graft commonly used with the Heartmate II and HVAD. This novel design allows for the possibility of less invasive implantation, through subcostal or thoracotomy incisions, and in some cases,

Table 1 Summary of LVAD trials demonstrating ongoing survival improvements

Author, reference	Year	Device	Number of patients	1 year survival (%)
Rose *et al.* (5)	2001	Pulsatile Heartmate	68	52
Miller *et al.* (11)	2007	Heartmate II	133	68
Pagani *et al.* (12)	2009	Heartmate II	281	73
Slaughter *et al.* (15)	2009	Heartmate II	134	68
John *et al.* (14)	2011	Heartmate II	1,496	85
Starling *et al.* (13)	2011	Heartmate II	169	85
Aaronson *et al.* (17)	2012	Heartware HVAD	140	86
Slaughter *et al.* (31)	2013	Heartware HVAD	332	84
Strueber *et al.* (16)	2014	Heartware HVAD	254	85

LVAD, left ventricular assist devices; HVAD, Heartware VAD.

without the need for cardiopulmonary bypass (19,20). These techniques have been reported to decrease need for intraoperative blood transfusions and intensive care unit (ICU) length of stay in patients with a prior sternotomy (19,21,22). Although several single-center and multi-center studies have indicated that the Jarvik 2000 provides safe, effective MCS for heart failure patients (21,23-30) which in some cases compared favorably with Heartmate II recipients (21) these studies' authors also indicated that the Jarvik 2000 functions optimally as an adjunct to native left ventricular function, with only partial unloading of the ventricle. Thus, although clinical experience indicates the ability of the Jarvik 2000 to provide full cardiac output if necessary (7,23,24), its maximal clinical benefit lies in its ability to augment left ventricular function and preserving as much native function as possible, which limits its application in some heart failure patients being considered for LVAD implantation.

More recently, CF-LVAD outcomes have continued to improve as our collective experience implantation and post-operative care has grown (*Table 1*). A retrospective multi-center analysis comparing patients implanted with a Heartmate II LVAD after FDA approval in commercial use with the results from the clinical trial reported a consistent improvement in outcomes (14), with an increase in the percentage of patients who were either transplanted, explanted, or receiving ongoing LVAD support at 6 months and 1 year in the posttrial cohort. Similarly, recently reported figures from patients implanted with the HVAD have also shown remarkable improvements in outcomes, with survival now exceeding 90% at 1 year (31). In fact, the increased utilization of CF-LVADs, along with their excellent long-term outcomes, have led to a decrease in the number of patients transplanted in the first year, from 48% during the Heartmate II BTT clinical trial to only 39% during the post-trial period (14). In this same period, one year survival on the heart transplant waiting list actually increased despite the decreased transplantation rate. This indicates an increase in the number and proportion of patients awaiting heart transplantation after LVAD implantation, further highlighting the feasibility and reliability of extended LVAD support.

As results in patients receiving LVADs as a BTT have continued to improve, even rivaling the results seen in heart transplant recipients (32), a national discourse has begun on whether to re-evaluate the current status criteria for listing patients implanted with a LVAD on the United Network for Organ Sharing (UNOS) for cardiac transplantation. However, an equally compelling question is how LVAD implantation impacts heart transplant outcomes. Previously reported outcomes have been conflicting with regard to the impact LVAD implantation has on post-cardiac transplantation survival (33-37). In addition, optimal duration of VAD support prior to cardiac transplantation remains unknown (38,39) with some data suggesting adverse post-transplant survival in patients who required prolonged LVAD support prior to cardiac transplant (33,35-37,40,41). However, more recent data suggests that post-transplant mortality is not adversely affected by the duration of LVAD support (34), even in patients who were supported for over one year prior to transplant. In support of this, contemporary results appear to suggest that BTT patients implanted with CF-LVADs do not have significantly different post-transplant survival rates or adverse outcomes (42).

Complications

While inherent device malfunction or failure has been virtually eliminated in the modern era with the development of reliable CF devices, major adverse events continue to be a significant concern. Bleeding, infection, stroke, malignant arrhythmias, and pump thrombosis continue to be valid concerns requiring ongoing monitoring and vigilance. Perhaps surprisingly given the improvements in patient survival and lessons learned regarding the management of CF-LVAD patients in the modern era, the percentage of patients who required upgrading to status 1A because of an LVAD-related complication has not changed significantly since its introduction and remains at almost 30% of patients on LVAD support (43).

Early concerns regarding the long-term effects of low systemic arterial pulsatility on end-organ dysfunction have largely been refuted (44). Nevertheless, the lack of pulsatility in CF-LVAD devices does pose some unique challenges in the management of patients in the clinical setting and may be responsible for some of the changes in vascular endothelial function and tone observed in patients supported with CF LVADs.

The decrease in pulse pressure observed in CF-LVADs is primarily related to augmentation of diastolic blood flow. Due to the continuous unloading of the left ventricle with CF-LVADs, increased blood flow during diastole leads to an increase in diastolic blood pressure. Pump speed settings must be carefully monitored and adjusted to provide the appropriate unloading of the left ventricle. Pump speed settings that are high may result in collapse of the left ventricle, leading to a "suck-down" effect on the ventricle, causing obstruction of the inflow cannula and, potentially, malignant ventricular arrhythmias. In addition, continuous unloading of the left ventricle can potentially lead to decreased aortic valve opening and increased trans-aortic pressure gradients. Aortic insufficiency has been observed in patients requiring a prolonged duration of support, with increased frequency and severity reported when the aortic valve remains closed for prolonged periods (45-48).

The lack of pulsatility in CF devices also appears to cause histologic changes in the endothelium. Disruption of the renin-angiotensin system, altered responses to vasopressors, and medial arterial wall thickening with changes in the smooth muscle and elastin content have all been demonstrated as consequences of decreased pulsatility (49-52). These changes may be responsible for the reported increase in hemodynamic compromise observed in patients on prolonged CF device support, as demonstrated by an increase in the required dose and duration of press or support after cardiac transplantation (53).

Additionally, gastrointestinal bleeding [occurring in up to 40% of CF LVAD patients (54)] appears to be at least partially caused by the lack of pulsatility, thought to be responsible for the formation of angiodysplasias and arteriovenous malformations. First reported in 2005 by Letsou *et al.* (55), the association of gastrointestinal bleeding with CF-LVADs remains a concern. Further study to determine the etiology of this phenomenon led some observant investigators to notice a similarity to a physiologic state observed in patients with aortic stenosis (56). Aortic stenosis patients, who also exhibit a narrow pulse pressure similar to that seen in patients on CF-LVAD support, are thought to develop an "acquired von Willebrand disease" leading to gastrointestinal bleeding episodes (57). The finding that has garnered the most attention is the loss of large von Willebrand factor (vWF) multimers, much like Heyde syndrome as described in patients with critical aortic stenosis (58). Veyradier *et al.* (59) noted a high rate of von Willebrand disease in non-VAD patients with bleeding angiodysplasia and proposed that this deficiency was particularly pertinent at the very high shear conditions related to these malformations. In sharp contrast to heart transplant recipients, Geisen *et al.* (60) first reported loss of large vWF multimers in patients supported with Heartmate II and pulsatile VADs despite amounts of vWF antigen that were comparable to that seen in heart transplant recipients. Taken together, the evidence of acquired von Willebrand disease in the CF-VAD population is compelling and likely a key contributor to the pathophysiology of gastrointestinal bleeding. However, the fact that not all CF-VAD patients experience bleeding complications implies that other factors are also critical.

Finally, infectious complications continue to be an important risk factor for long-term survival (61). In fact, a recent UNOS analysis found that device-related infectious complications led to decreased post-transplant mortality (62). Therefore, prevention strategies, including patient education and aggressive, early treatment of driveline infections, are paramount. As trauma to the percutaneous lead exit site may be a potential cause of many device-related infections, preventative stabilization of the lead is an important prevention strategy to minimize post-operative infectious risk.

Future directions

When the clinical trials with CF LVADs began just over a decade ago, there was concern over the uncertainty of the long-term effects of arterial blood flow with low pulsatility (63). However, the large amount of cumulative experience with CF-VADS indicates that long-term support does not carry detrimental effects on organ function (44). Although it appears that the reliability issues of the past have been largely addressed with the newer CF-LVADs, some adverse events continue to limit the overall effectiveness of the technology. Although infection rates have decreased with the smaller LVADs now being implanted, infection continues to be an important risk factor for long-term survival (62). Aggressive strategies for prevention and treatment of infection need to be refined. Because antibiotic-resistant organisms are the frequent source of many device-related infections (61), preventative measures are likely to have the greatest impact on infection rates. For long durations, a totally implantable LVAD with a transcutaneous energy transmission system may offer the best option for preventing infection (64).

Experience from the clinical trials and post-trial studies with CF pumps have yielded several additional lessons about patient selection, perioperative management, operative technique, and long-term management of these patients. Looking forward, there are several areas of potential progress in our efforts to reduce the risks of bleeding and thrombosis in patients with contemporary CF-VADs. The availability of oral direct thrombin inhibitors is one such opportunity. Preliminary studies in other populations have suggested an acceptable and potentially improved safety profile compared with vitamin K antagonists (65), but the higher risk of bleeding in CF-VAD patients coupled with the difficulty of prompt reversal of these agents must be carefully considered. Finally, noninvasive analytics such as acoustic signature analysis may provide an opportunity to diagnose pump thrombosis earlier in the course of development (66), when aggressive anticoagulation may be sufficient to prevent progression and the need for surgical pump exchange.

Future generation devices close to clinical trials include Thoratec's HeartMate III and Heartware's MVAD Pump. The Heartmate III is a CF centrifugal pump that is magnetically levitated pump that may have a more favorable blood pump contact profile (67). In addition to increased miniaturization compared to the HM II, the HM III features improved flow dynamics which may limit shear forces compared to current CF-LVADs (68). The MVAD pump is a continuous axial flow pump, approximately one-third the size of the HVAD Pump. The MVAD Pump is based on the same proprietary "contactless" impeller suspension technology used in the HVAD Pump, with its single moving part held in place through a combination of passive-magnetic and hydrodynamic forces. The MVAD Pump is designed to support a wide range of flows to enable both full and partial support capability.

Conclusions

CF-LVAD has become the therapeutic standard for management of advanced heart failure in patients awaiting heart transplantation with excellent outcomes reported which continue to improve over time. Initial pulsatile flow LVADs had significant device related complications and device failure, limiting its widespread acceptance. The significant early mortality risk [up to 30% in the first three weeks (69)] led to a UNOS cardiac allocation policy allowing for 1A status for thirty days following LVAD implantation, and permanent 1B status thereafter. However, with improvements in LVAD outcomes, as well data that suggested increased mortality in LVAD-bridged transplant patients receiving transplants within 1 month after pulsatile LVAD implant (38,39,69), the policy was modified in 2002 to allow for thirty days of 1A status at any timepoint after LVAD implantation at the physician's discretion (69,70). In the contemporary era, outcomes have improved to the point that patients supported with CF-LVADs as a BTT have similar mortality risk as patients listed as status 2 and may even have improved survival (43).

Complications related to LVAD implantation have improved as well, but remain a significant cause for concern. While non-device related adverse events from CF-LVADs appear to occur at lower rates than in their pulsatile counterparts (12), the risk is hardly eliminated and complications specific to CF-LVADs are now being seen. It appears the highest risk for complications occurs peri-operatively, with a rapid decrease within two months after LVAD implantation (43).

Our institution's experience with CF-LVAD compare favorably to those reported at other centers (71). Similar to results published from other groups nationally, we have observed significant improvements in baseline hemodynamics (42) and excellent survival outcomes, both in patients receiving ongoing LVAD support as well as after cardiac transplant (42,71). In addition, while gastrointestinal bleeding remains a concern in patients implanted with

CF-LVADs at our institution, very few devices have required replacement due to device thrombosis, malfunction, or infection and no mechanical failures have been reported (71). As our center's experience approaches 300 patients implanted with the Heartmate II LVAD, the reliability, durability, and improvements in survival and quality of life in heart failure patients implanted with CF-LVADs, have provided us with a viable surgical strategy for the growing number of patients awaiting heart transplantation.

The increased acceptance and utilization of CF-LVADs will likely lead to continued improvement in patient outcomes through increased clinical experience and device design. Although LVAD-related complications requiring status 1A listing continues to occur at a high rate, contemporary results for BTT patients on LVAD support may lead to revision of the current UNOS allocation policy regarding cardiac transplantation to assure the most equitable and appropriate priority for listing of heart transplant eligible patients.

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References

1. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:399-410.
2. Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327-36; discussion 336-8.
3. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the thoratec ventricular assist device as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1997;113:202-9.
4. Frazier OH, Rose EA, Oz MC, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J Thorac Cardiovasc Surg 2001;122:1186-95.
5. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.
6. Dembitsky WP, Tector AJ, Park S, et al. Left ventricular assist device performance with long-term circulatory support: lessons from the REMATCH trial. Ann Thorac Surg 2004;78:2123-9; discussion 2129-30.
7. John R. Current axial-flow devices--the HeartMate II and Jarvik 2000 left ventricular assist devices. Semin Thorac Cardiovasc Surg 2008;20:264-72.
8. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873-84.
9. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.
10. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation 2007;116:497-505.
11. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885-96.
12. Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol 2009;54:312-21.
13. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890-8.
14. John R, Naka Y, Smedira NG, et al. Continuous flow left ventricular assist device outcomes in commercial use compared with the prior clinical trial. Ann Thorac Surg 2011;92:1406-13; discussion 1413.
15. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.
16. Strueber M, Larbalestier R, Jansz P, et al. Results of the post-market Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE). J Heart Lung Transplant 2014;33:486-91.
17. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200.
18. Lindenfeld J, Feldman AM, Saxon L, et al. Effects of

cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation 2007;115:204-12.
19. Frazier OH, Gregoric ID, Cohn WE. Initial experience with non-thoracic, extraperitoneal, off-pump insertion of the Jarvik 2000 Heart in patients with previous median sternotomy. J Heart Lung Transplant 2006;25:499-503.
20. Selzman CH, Sheridan BC. Off-pump insertion of continuous flow left ventricular assist devices. J Card Surg 2007;22:320-2.
21. Sorensen EN, Pierson RN 3rd, Feller ED, et al. University of Maryland surgical experience with the Jarvik 2000 axial flow ventricular assist device. Ann Thorac Surg 2012;93:133-40.
22. Sun BC, Firstenberg MS, Louis LB, et al. Placement of long-term implantable ventricular assist devices without the use of cardiopulmonary bypass. J Heart Lung Transplant 2008;27:718-21.
23. Frazier OH, Myers TJ, Gregoric ID, et al. Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system. Circulation 2002;105:2855-60.
24. Frazier OH, Myers TJ, Westaby S, et al. Use of the Jarvik 2000 left ventricular assist system as a bridge to heart transplantation or as destination therapy for patients with chronic heart failure. Ann Surg 2003;237:631-6; discussion 636-7.
25. Frazier OH, Myers TJ, Westaby S, et al. Clinical experience with an implantable, intracardiac, continuous flow circulatory support device: physiologic implications and their relationship to patient selection. Ann Thorac Surg 2004;77:133-42.
26. Haj-Yahia S, Birks EJ, Rogers P, et al. Midterm experience with the Jarvik 2000 axial flow left ventricular assist device. J Thorac Cardiovasc Surg 2007;134:199-203.
27. Myers TJ, Robertson K, Pool T, et al. Continuous flow pumps and total artificial hearts: management issues. Ann Thorac Surg 2003;75:S79-85.
28. Siegenthaler MP, Frazier OH, Beyersdorf F, et al. Mechanical reliability of the Jarvik 2000 Heart. Ann Thorac Surg 2006;81:1752-8; discussion 1758-9.
29. Siegenthaler MP, Westaby S, Frazier OH, et al. Advanced heart failure: feasibility study of long-term continuous axial flow pump support. Eur Heart J 2005;26:1031-8.
30. Westaby S, Banning AP, Saito S, et al. Circulatory support for long-term treatment of heart failure: experience with an intraventricular continuous flow pump. Circulation 2002;105:2588-91.
31. Slaughter MS, Pagani FD, McGee EC, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2013;32:675-83.
32. Williams ML, Trivedi JR, McCants KC, et al. Heart transplant vs left ventricular assist device in heart transplant-eligible patients. Ann Thorac Surg 2011;91:1330-3; discussion 1333-4.
33. Cleveland JC Jr, Grover FL, Fullerton DA, et al. Left ventricular assist device as bridge to transplantation does not adversely affect one-year heart transplantation survival. J Thorac Cardiovasc Surg 2008;136:774-7.
34. John R, Pagani FD, Naka Y, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg 2010;140:174-81.
35. Morgan JA, Park Y, Kherani AR, et al. Does bridging to transplantation with a left ventricular assist device adversely affect posttransplantation survival? A comparative analysis of mechanical versus inotropic support. J Thorac Cardiovasc Surg 2003;126:1188-90.
36. Patlolla V, Patten RD, Denofrio D, et al. The effect of ventricular assist devices on post-transplant mortality an analysis of the United network for organ sharing thoracic registry. J Am Coll Cardiol 2009;53:264-71.
37. Robertson JO, Lober C, Smedira NG, et al. One hundred days or more bridged on a ventricular assist device and effects on outcomes following heart transplantation. Eur J Cardiothorac Surg 2008;34:295-300.
38. Ashton RC Jr, Goldstein DJ, Rose EA, et al. Duration of left ventricular assist device support affects transplant survival. J Heart Lung Transplant 1996;15:1151-7.
39. Gammie JS, Edwards LB, Griffith BP, et al. Optimal timing of cardiac transplantation after ventricular assist device implantation. J Thorac Cardiovasc Surg 2004;127:1789-99.
40. Aaronson KD, Eppinger MJ, Dyke DB, et al. Left ventricular assist device therapy improves utilization of donor hearts. J Am Coll Cardiol 2002;39:1247-54.
41. Jaski BE, Kim JC, Naftel DC, et al. Cardiac transplant outcome of patients supported on left ventricular assist device vs. intravenous inotropic therapy. J Heart Lung Transplant 2001;20:449-56.
42. Kamdar F, John R, Eckman P, et al. Postcardiac transplant survival in the current era in patients receiving continuous-flow left ventricular assist devices. J Thorac Cardiovasc Surg 2013;145:575-81.

43. Wever-Pinzon O, Drakos SG, Kfoury AG, et al. Morbidity and mortality in heart transplant candidates supported with mechanical circulatory support: is reappraisal of the current United network for organ sharing thoracic organ allocation policy justified? Circulation 2013;127:452-62.
44. Russell SD, Rogers JG, Milano CA, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation 2009;120:2352-7.
45. Cowger J, Pagani FD, Haft JW, et al. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail 2010;3:668-74.
46. John R, Mantz K, Eckman P, et al. Aortic valve pathophysiology during left ventricular assist device support. J Heart Lung Transplant 2010;29:1321-9.
47. Jorde UP, Uriel N, Nahumi N, et al. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. Circ Heart Fail 2014;7:310-9.
48. Pak SW, Uriel N, Takayama H, et al. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. J Heart Lung Transplant 2010;29:1172-6.
49. Lou X, Templeton DL, John R, et al. Effects of continuous flow left ventricular assist device support on microvascular endothelial function. J Cardiovasc Transl Res 2012;5:345-50.
50. Nishimura T, Tatsumi E, Nishinaka T, et al. Diminished vasoconstrictive function caused by long-term nonpulsatile left heart bypass. Artif Organs 1999;23:722-6.
51. Travis AR, Giridharan GA, Pantalos GM, et al. Vascular pulsatility in patients with a pulsatile- or continuous-flow ventricular assist device. J Thorac Cardiovasc Surg 2007;133:517-24.
52. Westaby S, Bertoni GB, Clelland C, et al. Circulatory support with attenuated pulse pressure alters human aortic wall morphology. J Thorac Cardiovasc Surg 2007;133:575-6.
53. Stewart AS, Russo MJ, Martens TP, et al. Longer duration of continuous-flow ventricular assist device support predicts greater hemodynamic compromise after return of pulsatility. J Thorac Cardiovasc Surg 2008;136:524-5.
54. Stern DR, Kazam J, Edwards P, et al. Increased incidence of gastrointestinal bleeding following implantation of the HeartMate II LVAD. J Card Surg 2010;25:352-6.
55. Letsou GV, Shah N, Gregoric ID, et al. Gastrointestinal bleeding from arteriovenous malformations in patients supported by the Jarvik 2000 axial-flow left ventricular assist device. J Heart Lung Transplant 2005;24:105-9.
56. Heyde E. Gastrointestinal bleeding in aortic stenosis [letter to the editor]. N Engl J Med 1958;259:196.
57. Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link? Lancet 1992;340:35-7.
58. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343-9.
59. Veyradier A, Balian A, Wolf M, et al. Abnormal von Willebrand factor in bleeding angiodysplasias of the digestive tract. Gastroenterology 2001;120:346-53.
60. Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg 2008;33:679-84.
61. Topkara VK, Kondareddy S, Malik F, et al. Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. Ann Thorac Surg 2010;90:1270-7.
62. Healy AH, Baird BC, Drakos SG, et al. Impact of ventricular assist device complications on posttransplant survival: an analysis of the United network of organ sharing database. Ann Thorac Surg 2013;95:870-5.
63. Thalmann M, Schima H, Wieselthaler G, et al. Physiology of continuous blood flow in recipients of rotary cardiac assist devices. J Heart Lung Transplant 2005;24:237-45.
64. Asgari SS, Bonde P. Implantable physiologic controller for left ventricular assist devices with telemetry capability. J Thorac Cardiovasc Surg 2014;147:192-202.
65. Salazar CA, del Aguila D, Cordova EG. Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with non-valvular atrial fibrillation. The Cochrane database of systematic reviews 2014;3:CD009893.
66. Uriel N, Morrison KA, Garan AR, et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. J Am Coll Cardiol 2012;60:1764-75.
67. Farrar DJ, Bourque K, Dague CP, et al. Design features, developmental status, and experimental results with the Heartmate III centrifugal left ventricular assist system with a magnetically levitated rotor. ASAIO J 2007;53:310-5.
68. Farrar DJ, Bourque K, Reichenbach SH, et al. Innovation Update. In: Kyo S. eds. Ventricular assist devices in advanced-stage heart failure. Springer, 2014.
69. Renlund DG, Taylor DO, Kfoury AG, et al. New

UNOS rules: historical background and implications for transplantation management. United Network for Organ Sharing. J Heart Lung Transplant 1999;18:1065-70.
70. Moazami N, Sun B, Feldman D. Stable patients on left ventricular assist device support have a disproportionate advantage: time to re-evaluate the current UNOS policy. J Heart Lung Transplant 2011;30:971-4.
71. John R, Kamdar F, Eckman P, et al. Lessons learned from experience with over 100 consecutive HeartMate II left ventricular assist devices. Ann Thorac Surg 2011;92:1593-9; discussion 1599-600.

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Review Article

Adult heart transplant: indications and outcomes

M. Chadi Alraies, Peter Eckman

Department of Medicine, Division of Cardiovascular Medicine, University of Minnesota, Minneapolis, MN, USA

Correspondence to: Peter Eckman, MD. Department of Medicine, Division of Cardiovascular Medicine, University of Minnesota, Minneapolis, MN, USA. Email: eckmanp@umn.edu.

Abstract: Cardiac transplantation is the treatment of choice for many patients with end-stage heart failure (HF) who remain symptomatic despite optimal medical therapy. For carefully selected patients, heart transplantation offers markedly improved survival and quality of life. Risk stratification of the large group of patients with end-stage HF is essential for identifying patients who are most likely to benefit, particularly as the number of suitable donors is insufficient to meet demand. The indications for heart transplant and review components of the pre-transplant evaluation, including the role for exercise testing and risk scores such as the Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM) are summarized. Common contraindications are also discussed. Outcomes, including survival and common complications such as coronary allograft vasculopathy are reviewed.

Keywords: Heart transplant; indications; outcomes

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Introduction

Congestive heart failure (CHF) affects 23 million people worldwide including 7.5 million in North America. The prevalence of HF in the US population age 20 and older is 2.6% (1). Half of these patients have systolic dysfunction. Cardiac transplantation is the treatment of choice for many patients with end-stage HF who remain symptomatic despite optimal medical therapy (2). The annual mortality rate while on the waiting list in 2001 was 17%, which has declined continually over the last decade to 13.7% in 2009 (3), likely from improved medical therapy for end-stage CHF and increased use of implantable cardioverter-defibrillator and cardiac resynchronization therapy (3,4). Long-term outcomes after transplantation have improved with the advances made in transplant candidate selection, surgical techniques, immunosuppressive modalities, and postoperative care (5,6). The International Society for Heart and Lung Transplantation (ISHLT) registry has reported 89,000 heart transplants worldwide since 1983; there is broad agreement that underreporting is present and the actual number is higher (7). The total number of cardiac transplant likely exceeds 5,000 worldwide with current median survival rate as approximately 50% at 12 years (7). Nevertheless, there are far more eligible candidates than suitable donor organs. Risk stratification of the large group of patients with end-stage HF is essential for identifying patients who are most likely to benefit (8).

Patients with advanced HF are classified into two systems based on the severity; New York Heart Association Class which classifies patients by their functional status, from I (no limitation in activities) to IV (symptoms at rest). NYHA class III (symptoms with minimal exertion) and NYHA class II mild shortness of breath limiting ordinary activity (9). The other system was generated by joint American College of Cardiology and American Heart Association (ACC/AHA) classification uses four stages, from A (high risk of developing HF, i.e., family history of heart disease, hypertension, or diabetes) to D (advanced heart disease despite treatment) (9-11). Patients in stage D tend to require recurrent hospitalization despite cardiac resynchronization therapy and drug therapy, and they cannot be safely discharged without specialized interventions (12). The options for these patients are limited: either end-of-life care or extraordinary measures such as heart transplantation, long-term treatment with inotropic drugs, permanent mechanical

circulatory support, or experimental therapies (9). The estimated number of people in ACC/AHA stage D or NYHA class IV is 15,600 to 156,000 (7). Heart transplant in patients with inadequate response to medical therapy has been shown to extend survival and improve quality of life.

Who is considered for heart transplant?

In general, patients with advanced HF should be considered for heart transplantation if optimal medical therapy as recommended by the ACC/AHA guidelines and cardiac resynchronization therapy have failed to improve symptoms or halt progression of the underlying pathology (9,12-14). Furthermore, any reversible or surgically amenable cardiac conditions should be addressed before transplantation is considered. The latter is important to guarantee the candidacy for heart transplant and reserve organs for the more needed patients. Patients who are in advanced NYHA class IV need evaluation by advanced HF teams for optimal management of multi-organ failure (9,15). Patients with severe HF have a 1 to 2 year mortality rate approaching 50%, despite advanced medical treatment (7,16). The primary indications for heart transplantation for adult patients have been nonischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%). Other indications include: valvular heart disease (3%), retransplantation (3%) and others (<1%) (7,8,17).

Indications for heart transplantation

The ACC/AHA guidelines include the following indications for cardiac transplantation (11):

- Refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation or left ventricular assist device (LVAD);
- Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.);
- Peak VO_2 (VO_{2max}) less than 10 mL/kg per min;
- NYHA class of III or IV despite maximized medical and resynchronization therapy;
- Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation;
- End-stage congenital HF with no evidence of pulmonary hypertension;
- Refractory angina without potential medical or surgical therapeutic options.

Similarly, the European Society of Cardiology describes a series of features that must be met before consideration for heart transplant which are more specific and include, functional, structural and symptoms parameters (18);

- Severe symptoms, with dyspnea at rest or with minimal exertion (NYHA class III or IV);
- Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion);
- Objective evidence of severe cardiac dysfunction (at least one of the following): left ventricular ejection fraction less than 30%, pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography, high left and/or right ventricular filling pressure severely impaired functional capacity demonstrated by one of the following: inability to exercise, 6-minute walk test distance less than 300 m (or less in women or patients who are age 75 and older), or peak oxygen intake less than 12 to 14 mL/kg/min;
- One or more hospitalizations for HF in the past 6 months.

Pre-transplantation evaluation

Many of the criteria defining eligibility for heart transplant are somewhat subjective, and focused primarily on resting hemodynamic data and NYHA classification. However, a substantial percentage of patients with severe resting hemodynamic abnormalities may survive for extended periods. Furthermore, NYHA classification as a measure of functional capacity is a subjective and frequently inaccurate index, which can vary from day to day depending on evanescent factors. Tools to improve risk stratification of HF patients are critical to ensure that only patients with a high probability of benefit are subjected to the risks of heart transplant. In patients with HF, several methods are typically employed to objectively estimate adverse prognosis with medical therapy alone.

Exercise capacity as assessed by peak VO_2 (VO_{2max})

Exercise capacity as assessed by VO_{2max} is a dynamic objective variable that assesses cardiac reserve and peripheral adaptations to a reduced cardiac output much more accurately than NYHA classification. It is generally considered the gold standard for establishing a severity of functional cardiac impairment that merits active consideration for transplant. Patients with preserved exercise capacity (peak exercise VO_2 of more than 14 mL/min/kg) despite severe resting

hemodynamic impairment, have survival and functional capacity equal to those afforded by cardiac transplantation (19,20). Moreover, patients with compensated CHF and a peak oxygen consumption of less than 14 mL/kg/min or <50% predicted are considered sufficiently impaired for transplantation (9,11,21). This approach suggests that cardiac transplantation can be safely deferred in ambulatory patients with severe left ventricular dysfunction and a peak oxygen consumption of greater than 14 mL/kg/min. Beta blocker therapy has improved survival rates in patients with systolic HF including patients with very low VO_{2max} to as low as 10 mL/kg per min. The prognostic power of VO_{2max} was initially validated prior to the widespread use of beta blockers, but several studies have demonstrated the continued usefulness of VO_2 in the modern drug era with beta blocker use (5,21). With the current evidence-based HF therapy including beta-blockers, spironolactone, angiotensin converting enzyme inhibitors and devices (i.e., implantable cardioverter-defibrillator and cardiac resynchronization therapy), a VO_{2max} ≤10 mL/kg/min rather than the traditional cutoff value ≤14 mL/min/kg may be more useful for risk stratification in the device era (20). More recent work has suggested that ventilatory efficiency (VE/VCO_2) may be a more powerful prognostic factor than VO_{2max} (22,23). Ventilatory efficiency also appears to be more effective in risk stratification for patients with inadequate peak respiratory exchange ratios (RERs), which are used to confirm that anaerobic threshold has been achieved (24). Finally, ventilatory efficiency has been shown to maintain prognostic value regardless of body mass index, another potential confounding factor that can limit interpretation of VO_{2max} (25).

Cardiopulmonary exercise testing is a relatively specialized test, and is not routinely available outside of transplant centers. It would also be expensive and impractical to screen all HF patients with full exercise testing. Exercise testing also provides a single perspective of performance and prognosis. To meet this need, several risk scores have been developed to help clinicians identify HF patients whose severity of illness is sufficient to merit consideration for transplant. The two best known and most widely used for the advanced HF population are the Heart Failure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM).

Heart Failure Survival Score (HFSS)

This score was derived from a multivariable analysis of 268 ambulatory patients referred for consideration of cardiac transplantation from 1986 to 1991 and validated in 199 similar patients from 1993 to 1995 (26). The predictors of survival in the HFSS include:

- Presence or absence of coronary artery disease;
- Resting heart rate;
- Left ventricular ejection fraction;
- Mean arterial blood pressure;
- Presence or absence of an intraventricular conduction delay on ECG;
- Serum sodium;
- VO_{2max}.

Scores are categorized into low-risk (score ≥8.1), medium-risk (score ≥7.2 and <8.1), and high-risk (<7.2). Patients in medium and high-risk groups (1-year survival of 72% and 43%, respectively) are most likely to die or require urgent transplant in the following year; they should be considered for cardiac transplantation if no contraindications are present. Transplantation can be safely deferred in patients in the low-risk group (1-year survival 93%). HFSS has been reported to outperform peak oxygen consumption for heart transplant selection in the current era of ventricular assist device therapy (20).

The Seattle Heart Failure Model (SHFM)

The SHFM gives an estimate of prognosis for ambulatory patients with advanced HF (27). This model is based on age, sex, NYHA class, weight, ejection fraction, blood pressure, medications, a few laboratory values, and other clinical information. Furthermore, the model has incorporated the impact of newer HF therapies on survival, including ICDs and CRT. The model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of clinical, pharmacologic, device, and laboratory characteristics. It is available on the internet (http://depts.washington.edu/shfm, accessed on 24 March 2014), and applications for handheld electronic devices. It also allows evaluation of the estimated effect of interventions on an individual patient's prognosis. The model also was able to provide information about the likely mode of death among ambulatory HF patients (28). SHFM was developed in an ambulatory HF population and there has been concern that it may overestimate survival in the advanced HF population (29,30). Nevertheless, it remains a useful method for estimating survival in HF patients.

Finally, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was recently noted to predict short- and long-term mortality after heart transplant (31).

Efforts to combine evaluation of risk of mortality from HF with prediction of outcome after transplant may offer opportunities to further improve the net outcomes after transplant through the development of a "cardiac allocation score" (32).

Heart transplant contraindications

Once the question of whether or not an individual is "sick enough" to merit consideration for transplant has been addressed, the next question that must be asked is whether or not the patient is "too sick" for transplant. Improving cardiac status only to die of hepatic failure would not be considered a judicious use of a truly scarce resource. The following circumstances are typically felt to be absolute contraindications to heart transplantation (9,11,33):

(I) Advanced irreversible renal failure with Cr >2 or creatinine clearance <30-50 mL/min without plans for concurrent renal transplant;
(II) Advanced irreversible liver disease;
(III) Advanced irreversible pulmonary parenchymal disease or (FEV_1 <1 L/min);
(IV) Advanced irreversible pulmonary artery hypertension (pulmonary artery systolic pressure >60 mmHg, pulmonary vascular resistance >4-5 wood units despite vasodilators) due to risk of acute right ventricular failure soon after transplant from insufficient accommodation of the donor heart to high pulmonary vascular resistance pressures;
(V) History of solid organ or hematologic malignancy within the last 5 years due to probability of recurrence.

The following are generally considered relative contraindications for heart transplant due to the reversibility of the disease or due to lack of direct impact on the transplanted organ (33).

(I) Severe peripheral vascular disease;
(II) Severe cerebrovascular disease;
(III) Severe osteoporosis;
(IV) Severe obesity (BMI >35 kg/m^2) or cachexia;
(V) Acute pulmonary embolism;
(VI) Active infection (excluding LVAD-related infections);
(VII) Advanced age (>70 years old);
(VIII) Psychological instability (e.g., PTSD);
(IX) Active or recent (within 6 months) substance abuse (alcohol, cocaine, opioids, tobacco products, etc.);
(X) Diabetes mellitus with end organ damage;
(XI) Lack of social support or sufficient resources to permit ongoing access to immunosuppressive medication and frequent medical follow-up.

Allosensitization to human leukocyte antigen (HLA) antibodies can pose a particular problem, and may also preclude transplant eligibility. Further details on this topic are beyond the scope of this work, but have been recently reviewed elsewhere (34,35).

The United Network of Organ Sharing (UNOS) and heart transplant listing

Based on their medical condition, UNOS assigns all transplant candidates a status (3,36). The highest status, 1A, goes to patients who are seriously ill, in the hospital, on high doses of inotropic drugs (specific dosages are defined) and mechanical circulatory support such as an LVAD, and expected to live less than 1 month without a transplant. Status 1B patients are stable on lower-dose inotropic therapy or on mechanical support, and can be in the hospital or at home. Status 2 patients are stable and ambulatory and are not on inotropic drugs. Priority is given to patient with status 1A and those who have been waiting the longest. The national median waiting time by UNOS status at listing from 2003 to 2004 data is as follows: 49 days for status 1A, 77 days for status 1B, and 308 for status 2 patients. However, this heavily influenced by several factors. For example, patients with blood type O wait significantly longer than patients with other blood types such as blood type AB. Blood type O patients who are on status 2 can wait years for a suitable donor organ, and for all practical purposes, are listed in name only without realistic chance of transplant without change in priority as a result of deterioration in medical status. Due to the scarcity of donor organs and growing transplant waiting lists, it is crucial that cardiac transplant program adequately screen and properly select potential transplant recipients. Effective use of this limited resource is essential; to avoid "wasting" organs that become available for suboptimal recipients. The IMPACT score (31) was recently developed and validated from UNOS data to help estimate survival after cardiac transplant.

Management of patients on the waiting list

There has been significant development and ongoing research in to improve the management of HF patients

who are considered for transplant. These areas are focused around the continued improvement in outcomes with LVAD technologies for the management of patients on the transplant waiting list, or as an alternative to transplantation in patients who are not candidates for transplantation.

Mechanical circulatory support

Mechanical circulatory support is indicated for patients who are listed for transplant to keep them alive and functioning as well as possible while they are waiting (bridge to transplant). For others it is destination therapy since these patients are not candidates for a transplant, but a device may improve and prolong the rest of their life (37-39). However, there are approximately twofold more patients with advanced HF waiting for heart transplantation than available donors. Despite parallel advances in ventricular assist device therapy, approximately 8% of these patients die awaiting a suitable allograft (3,39). The role of mechanical circulatory support in patients eligible for transplant has increased tremendously over the last two decades. Data from the International Society of Heart and Lung Transplantation notes that 28% of transplant recipients between 2006 and 2012 had a ventricular assist device, a marked increase from 12% in 1992-2000 (40). Survival on the transplant waiting list was also recently demonstrated to be superior to survival on inotropes or intra-aortic balloon pump (41), suggesting that clinicians are increasingly using LVAD as a therapy that maximizes chance of survival for many candidates. Markedly improved survival following LVAD over the past decade has also increased enthusiasm for this option as a bridge to transplant. Finally, current UNOS organ allocation policy for candidates supported with LVAD may also be playing a role in the increased utilization (42).

Despite the improvements in outcomes after LVAD, the question of whether this confers increased risk after transplant has been critical. For example, the additional sternotomy alone might be expected to have an adverse impact on post-transplant outcomes. Fortunately, excellent short- and long-term post-cardiac transplant survival following LVAD in the current era has been reported (40,43), and duration of LVAD support does not appear to confer additional risk (44). UNOS data has also demonstrated similar post-transplant survival after LVAD, despite noting increased use of older donors in this population (45). Donneyong *et al.* also reported the results of a retrospective, propensity-matched analysis of UNOS data, in which use of HeartMate II prior to transplant was not associated with a statistically significant difference in 30 day or 1 year post-transplant mortality (46). Of note, an association was found between HeartMate II use prior to transplant and 64% lower risk of mortality among patients who survived beyond the first year after transplantation. However, another analysis of UNOS data found that adjusted 1-year post-transplantation mortality was higher among patients with LVADs compared to patients with inotropes (41), suggesting that the true impact of need for LVAD prior to transplant on outcome may require additional analysis.

Inotropic therapy

Inotropic drugs, which include intravenous dobutamine and milrinone, are used to help maintain end-organ function (9,47,48). This intervention can be used as a bridge until a patient can obtain a heart transplant or LVAD. Inotropic therapy is typically used for palliation and has been shown to increase the risk of mortality, which is about 50% at 6 months and nearly 100% at 1 year (9,47). A patient who requires inotrope infusion should be considered for hospice if they are not a candidate for a transplant or an assist device.

Heart transplant outcomes

Detailed information on heart transplant outcomes is published in an annual report by the International Society of Heart and Lung Transplant (40) and the reader is referred to this outstanding resource for additional information beyond the brief summary provided in this work.

Survival after heart transplantation is now excellent (33). The 1-year survival rate is about 90%, the 5-year rate is about 70%, but only about 20% survive 20 years or longer (12,16,49). Quality of life after heart transplantation is also generally excellent (15) and patients are frequently able to return to work, regardless of their profession (3,5,50). The leading cause of death after heart transplantation is malignancy, followed by coronary artery vasculopathy (CAV), then by graft failure. Some patients develop left ventricular dysfunction and HF of unknown cause. Others develop antibody-mediated rejection; in recent years this has been more promptly recognized, but treatment remains a challenge (1,6,34). Acute rejection, which used to be one of the main causes of death, now has a low incidence because of modern drug therapies.

Complications

The major causes of late morbidity and mortality are infections, chronic kidney disease, cardiac allograft vasculopathy (CAV), and malignancy (7). Adverse effects of immunosuppressive drugs continue to be problematic as well. These include infection, malignancy, osteoporosis, chronic kidney toxicity, hypertension, and neuropathy.

Coronary artery vasculopathy (CAV)

CAV was the largest problem when heart transplantation began and continues to be a major concern and focus of research (7,8). The precise molecular mechanism for the development of vasculopathy is not known. Both immune and nonimmune mechanisms have been implicated in the progression of vasculopathy. Coronary vasculopathy develops in 30% to 40% of heart transplant recipients within 5 years, and much over the years has not reduced the incidence. However, probably fewer than 5% of these patients die or even need bypass surgery or stenting, and the problem is managed the same as native atherosclerosis (17,51).

Infectious complications

Infection is common in organ transplant recipients. The types of infections expected in cardiac transplant recipients vary, depending on the time from transplantation. This is because the intensity of immunosuppression administered varies directly with the propensity for rejection, and the propensity to reject decreases over time. Bacteria and viruses account for more than 80% of infections after transplantation. The most common bacterial infections early after transplantation are nosocomial, caused by infected intravascular catheters or lines, or gram-negative pneumonias.

Renal dysfunction

Immunosuppressive therapy with calcineurin inhibitors has improved both graft function and survival in heart transplantation. However, calcineurin inhibitor-induced-induced nephrotoxicity still remains a serious clinical challenge. Chronic calcineurin inhibitor nephrotoxicity is characterized by a decrease in glomerular filtration rate (GFR), afferent arteriolopathy, and striped tubulointerstitial fibrosis. The greatest decline in GFR with cyclosporine occurs in the first 3 to 6 months (7). About 10% of heart transplant recipients develop stage four-kidney disease (with a GFR <30 mL/min) and need kidney transplantation or renal replacement therapy because of the use of calcineurin inhibitors for immunosuppression (52). Close monitoring of tacrolimus and cyclosporine blood levels is critically important to limit progressive decline in renal function, because there is no known treatment for preventing or reversing nephrotoxicity. At the time of transplantation, initiation of tacrolimus or cyclosporine is delayed postoperatively in patients at high risk for nephrotoxicity, and induction therapy (such as antithymocyte globulin or an IL-2 receptor antagonist such as basiliximab) may be used to permit delay or minimization of nephrotoxic calcineurin inhibitors.

Malignancy

Following heart transplantation, malignancy is identified in 3% to 18% of the recipients, with an estimated risk of 1% to 2% per year. It ranks second to coronary vasculopathy as a major cause of mortality, accounting for 10% to 23% of all deaths following heart transplantation (7,8). Cutaneous malignancy is the most common type, seen in up to 17% of patients, with a predominance of squamous cell carcinoma. Post-transplantation lymphoproliferative disorder (PTLD) is a frequently fatal complication, occurring in 1.7% to 6% of cardiac transplant recipients. The peak occurrence of PTLD is 3 to 4 months after transplantation. A strong association of PTLD with Epstein-Barr virus has been observed in several series. The use of OKT3, which may favorably affect the rejection rate, has been shown to increase the risk of lymphoma more than eightfold. This association remains contentious and has been challenged. OKT3 is rarely used in current clinical practice.

Conclusions

Heart transplantation is continuing to evolve with exciting new advancements in the preoperative, perioperative, and postoperative management of heart transplantation patients. Improvements in immunology and organ preservation are likely to further improve care. For carefully selected patients, heart transplantation offers markedly improved survival and quality of life. Novel immunosuppressive regimens and better understanding of immunobiology are keys to combat the ongoing issues of cardiac allograft rejection. In the years to come, limitations in donor organ availability and preservation,

along with immunosuppression, will be important areas for improvement. Newer, more technologically advanced mechanical assist devices, stem cell transplantation, and improved medical therapy are research areas that are growing exponentially and should continue to be explored as alternatives to transplantation in patients with HF. The future holds promise for many patients suffering from severe HF.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2011 update: A report from the american heart association. Circulation 2011;123:e18-e209.
2. Metra M, Ponikowski P, Dickstein K, et al. Advanced chronic heart failure: A position statement from the study group on advanced heart failure of the heart failure association of the european society of cardiology. Eur J Heart Fail 2007;9:684-94.
3. 2009 annual report of the U.S. organ procurement and transplantation network and the scientific registry of transplant recipients: Transplant data 1999-2008. U.S. department of health and human services, health resources and services administration, healthcare systems bureau, division of transplantation, rockville, MD. Available online: http://www.ustransplant.org/annual_reports/current/. Accessed February 1, 2014.
4. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. Circulation 2009;119:e391-479.
5. Butler J, Khadim G, Paul KM, et al. Selection of patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol 2004;43:787-93.
6. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: Analysis of organ procurement and transplantation network/U.S. united network of organ sharing data, 1990 to 2005. J Am Coll Cardiol 2007;50:1282-90.
7. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: Twenty-eighth adult heart transplant report--2011. J Heart Lung Transplant 2011;30:1078-94.
8. Starling RC. Advanced heart failure: Transplantation, LVADs, and beyond. Cleve Clin J Med 2013;80:33-40.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol 2013;62:e147-239.
10. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007-18.
11. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. Circulation 2009;119:1977-2016.
12. Russo MJ, Rana A, Chen JM, et al. Pretransplantation patient characteristics and survival following combined heart and kidney transplantation: An analysis of the united network for organ sharing database. Arch Surg 2009;144:241-6.
13. Shah MR, Starling RC, Schwartz Longacre L, et al. Heart transplantation research in the next decade--a goal to achieving evidence-based outcomes: National heart, lung, and blood institute working group. J Am Coll Cardiol 2012;59:1263-9.
14. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International society for heart and lung transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant 2006;25:1024-42.
15. Starling RC. Improved quantity and quality of life: A winning combination to treat advanced heart failure. J Am Coll Cardiol 2010;55:1835-6.
16. Russo MJ, Chen JM, Hong KN, et al. Survival after heart transplantation is not diminished among recipients with uncomplicated diabetes mellitus: An analysis of the united network of organ sharing database. Circulation 2006;114:2280-7.
17. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the international society for heart and lung transplantation: Twenty-sixth official adult heart transplant report-2009. J Heart Lung Transplant 2009;28:1007-22.
18. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and

chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69.
19. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778-86.
20. Goda A, Lund LH, Mancini D. The heart failure survival score outperforms the peak oxygen consumption for heart transplantation selection in the era of device therapy. J Heart Lung Transplant 2011;30:315-25.
21. O'Neill JO, Young JB, Pothier CE, et al. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation 2005;111:2313-8.
22. Bard RL, Gillespie BW, Lange DC, et al. Improving prognostic assessment of patients with advanced heart failure using ventilatory efficiency. J Heart Lung Transplant 2010;29:589-91.
23. Ferreira AM, Tabet JY, Frankenstein L, et al. Ventilatory efficiency and the selection of patients for heart transplantation. Circ Heart Fail 2010;3:378-86.
24. Chase PJ, Kenjale A, Cahalin LP, et al. Effects of respiratory exchange ratio on the prognostic value of peak oxygen consumption and ventilatory efficiency in patients with systolic heart failure. JACC Heart Fail 2013;1:427-32.
25. Chase P, Arena R, Myers J, et al. Relation of the prognostic value of ventilatory efficiency to body mass index in patients with heart failure. Am J Cardiol 2008;101:348-52.
26. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660-7.
27. Levy WC, Mozaffarian D, Linker DT, et al. The seattle heart failure model: Prediction of survival in heart failure. Circulation 2006;113:1424-33.
28. Mozaffarian D, Anker SD, Anand I, et al. Prediction of mode of death in heart failure: The seattle heart failure model. Circulation 2007;116:392-8.
29. Gorodeski EZ, Chu EC, Chow CH, et al. Application of the seattle heart failure model in ambulatory patients presented to an advanced heart failure therapeutics committee. Circ Heart Fail 2010;3:706-14.
30. Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G, et al. Utility of the seattle heart failure model in patients with advanced heart failure. J Am Coll Cardiol 2009;53:334-42.
31. Kilic A, Allen JG, Weiss ES. Validation of the united states-derived index for mortality prediction after cardiac transplantation (IMPACT) using international registry data. J Heart Lung Transplant 2013;32:492-8.
32. Smits JM, de Vries E, De Pauw M, et al. Is it time for a cardiac allocation score? first results from the eurotransplant pilot study on a survival benefit-based heart allocation. J Heart Lung Transplant 2013;32:873-80.
33. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation 2010;122:173-83.
34. Eckman PM. Immunosuppression in the sensitized heart transplant recipient. Curr Opin Organ Transplant 2010;15:650-6.
35. Eckman PM, Hanna M, Taylor DO, et al. Management of the sensitized adult heart transplant candidate. Clin Transplant 2010;24:726-34.
36. Organ procurement and transplantation network (OPTN). Organ distribution: Allocation of hearts and heart-lungs. Department of health and human services, health resources and services administration, healthcare systems bureau, division of transplantation. Available online: http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp
37. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.
38. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885-96.
39. Rosenbaum AN, John R, Liao KK, et al. Survival in elderly patients supported with continuous flow LVAD as bridge to transplant or destination therapy. J Card Fail 2014;20:161-7.
40. Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: Thirtieth official adult heart transplant report--2013; focus theme: Age. J Heart Lung Transplant 2013;32:951-64.
41. Wozniak CJ, Stehlik J, Baird BC, et al. Ventricular assist devices or inotropic agents in status 1A patients? Survival analysis of the United Network of Organ Sharing database. Ann Thorac Surg 2014;97:1364-71; discussion 1371-2.
42. Moazami N, Sun B, Feldman D. Stable patients on left ventricular assist device support have a disproportionate advantage: time to re-evaluate the current UNOS policy. J Heart Lung Transplant 2011;30:971-4.
43. Kamdar F, John R, Eckman P, et al. Postcardiac transplant survival in the current era in patients receiving continuous-flow left ventricular assist devices. J Thorac Cardiovasc Surg 2013;145:575-81.

44. John R, Pagani FD, Naka Y, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg 2010;140:174-81.
45. Taghavi S, Jayarajan SN, Komaroff E, et al. Continuous flow left ventricular assist device technology has influenced wait times and affected donor allocation in cardiac transplantation. J Thorac Cardiovasc Surg 2014;147:1966-71.
46. Donneyong M, Cheng A, Trivedi JR, et al. The association of pretransplant HeartMate II left ventricular assist device placement and heart transplantation mortality. ASAIO J 2014;60:294-9.
47. Gorodeski EZ, Chu EC, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. Circ Heart Fail 2009;2:320-4.
48. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. food and drug administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: A prospective study using the INTERMACS (interagency registry for mechanically assisted circulatory support). J Am Coll Cardiol 2011;57:1890-8.
49. Russo MJ, Davies RR, Sorabella RA, et al. Adult-age donors offer acceptable long-term survival to pediatric heart transplant recipients: An analysis of the united network of organ sharing database. J Thorac Cardiovasc Surg 2006;132:1208-12.
50. Blanche C, Blanche DA, Kearney B, et al. Heart transplantation in patients seventy years of age and older: A comparative analysis of outcome. J Thorac Cardiovasc Surg 2001;121:532-41.
51. WRITING GROUP MEMBERS, Lloyd-Jones D, Adams RJ, et al. Heart disease and stroke statistics--2010 update: A report from the american heart association. Circulation 2010;121:e46-e215.
52. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-40.

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Review Article

Heart-lung transplantation: pediatric indications and outcomes

Jonathan E. Spahr, Shawn C. West

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA 15224, USA; University of Pittsburgh School of Medicine, Pittsburgh, PA 15224, USA
Correspondence to: Jonathan E. Spahr, MD. Clinical Director, Pediatric Pulmonology, Children's Hospital of Pittsburgh of UPMC. Associate Professor of Pediatrics, University of Pittsburgh School of Medicine, 4221 Penn Avenue, Pittsburgh, PA 15224, USA. Email: jonathan.spahr@chp.edu; Shawn C. West, MD. Assistant Professor of Pediatrics, University of Pittsburgh School of Medicine. Heart and Heart-Lung Transplantation, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224, USA. Email: shawn.west@chp.edu.

Abstract: As indications for heart-lung transplant (HLT) have changed to some degree in the past 30 years, this treatment is being used less frequently in children due to more advanced care of severe heart and lung disease. This is fortunate as the outcomes for HLT are poor compared to other solid organ transplants and this is mainly due to the poorer outcome of the lung graft.

Keywords: Heart-lung transplant (HLT); pediatric; indications; outcomes

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Indications for pediatric heart lung transplantation (HLT)

The first HLT was performed in 1981 for a patient with primary pulmonary hypertension (PPHN) (1). The second HLT was performed for Eisenmenger's syndrome with unrepaired congenital heart disease. Indications for HLT remain similar today (2).

Combined heart double lung transplant is typically offered in cases with end-stage dysfunction of both the heart and the lungs (3). Multi-organ transplantation comes with increased risk to the patient and so heart transplantation (HT) or double lung transplantation (DLT) is considered instead of HLT and preferred when only one organ is affected to the extent of causing end-stage disease. HLT was performed in infants in the 1980s and 1990s for technical reasons instead of isolated heart or lung transplants, but this practice has largely disappeared as technical issues have been overcome with advances in surgery and greater expertise (4). In cases where patients have end-stage lung disease associated with or causing cardiac dysfunction, congenital heart disease with pulmonary hypertension, or congenital heart disease associated with pulmonary artery/vein abnormalities, HLT may be indicated (5,6). HLT may also be considered for retransplantation following either HT or lung transplantation. In the case of pulmonary hypertension, if cardiac function is preserved, DLT alone is indicated. In the case of pulmonary hypertension with severe right heart failure or left heart failure, HLT would then be indicated. It should be stressed that each case needs to be considered carefully and each organ closely scrutinized to determine the need for transplantation. The ability of the right heart to recover function can be difficult to predict and needs to have careful consideration when deciding the best option for the patient (HLT or DLT) (7). Care must be individualized as there are cases in which the stress of transplanting the "end-stage" organ would further compromise the function of the other and so it would be in the patient's best interest to perform HLT.

Evaluation for HLT typically occurs when a patient has an underlying disease compromising cardiac and pulmonary function and has a predicted survival of less than two years due to that underlying disease. A predicted survival of greater than two years would suggest that a patient would not derive a survival benefit from HLT and should not be listed for HLT given current outcomes (3). HLT is most indicated when patients have a survival expectancy of a few months to a year. Survival expectancy of less than a few months risks death while awaiting transplantation due to current wait times on the HLT list. Requiring inotropic support, mechanical ventilation, and/or mechanical circulatory support prior to transplant also lowers survival

Table 1 Indications for heart lung transplant by year of age from 1988-2013

Diagnoses	Age <1	Age 1-5	Age 6-10	Age 11-17	Total
All diagnoses	16	52	28	92	188
Eisenmenger's	2	6	2	20	30
Heart re-transplant	0	0	0	2	2
Alpha 1	0	0	0	1	1
Lung re-transplant	0	2	1	2	5
Alveolar proteinosis	1	0	0	0	1
PPHN	1	13	11	30	55
PVR	1	2	0	0	3
RCM	0	1	0	3	4
Other	4	4	3	7	18
CHD	5	13	4	15	37
Congenital	1	10	2	7	20
CF	0	1	4	4	9
DCM	1	0	1	1	3

Data obtained from Organ Transplant and Procurement Network, December 13, 2013. http://optn.transplant.hrsa.gov (6). Alpha 1, Alpha 1 antitrypsin deficiency; PPHN, primary pulmonary hypertension; PVR, pulmonary vascular disease; RCM, restrictive cardiomyopathy; CHD, congenital heart disease; CF, cystic fibrosis; DCM, dilated cardiomyopathy.

and should increase the urgency and priority for HLT. Candidates who are ambulatory and have adequate nutrition prior to transplantation derive better outcomes and so it is best to evaluate and list for HLT before severe, life-threatening complications arise. Body mass index and ideal body weight are parameters that can help determine whether HLT outcomes might be affected by poor nutrition (8). Finally, HLT should be considered if quality of life (QOL) is significantly impacted to the point that children are not able to participate in school or if they are dependent upon cardio-respiratory support that impinges upon QOL.

The three most common reasons in the United States for which patients have received a HLT since 1988 are PPHN (29%), congenital heart disease (CHD) (20%), and Eisenmenger's syndrome (16%); as shown in *Table 1* (9). By the ISHLT data, worldwide the most common reasons for which patients have received a HLT since 1986 are cystic fibrosis (28%), pulmonary hypertension (24%), congenital disease (22%), and Eisenmenger's syndrome (12%) (3). Other indications for HLT include heart re-transplantation, lung re-transplantation, alpha-1-antitrypsin deficiency, alveolar proteinosis, pulmonary vascular disease, restrictive cardiomyopathy, dilated cardiomyopathy, chronic obstructive pulmonary disease, and restrictive pulmonary disease. From 2000 to 2012, ISHLT data for diagnosis show more patients receive a HLT with an indication of cystic fibrosis in Europe than in North America. More patients receive a HLT with an indication of congenital heart disease in North America than in Europe (3).

Indications for isolated HT include lethal congenital heart disease in the newborn; end-stage congenital heart disease in the older child not amenable to palliative or corrective cardiac surgery; end stage cardiomyopathy; recurrent life threatening arrhythmias not controlled by medications, implanted defibrillator, or ablation; failure to wean from mechanical circulatory support; heart retransplantation; or other cardiac disease with a predicted survival less than 2 years (10). Since outcomes for DLT are poor in comparison to HT, HLT should only be considered if lung function is severely compromised and progressive in nature. The most common indications for isolated DLT are cystic fibrosis and pulmonary hypertension (3). Since cardiac function can be severely compromised by end-stage lung disease, HLT may need to be considered for those with severe primary lung disease that has affected cardiac function to the point that cardiac dysfunction is considered to be progressive and irreversible (7).

Contraindications for HLT include extra-cardiac disease such as severe end-organ disease (such as renal or hepatic disease), active/recent malignancy, HIV infection, or other

Table 2 Number of heart lung transplants performed by year and age

Age	1988-1992	1993-1997	1998-2002	2003-2007	2008-2013	All years
<1	2	2	8	4	0	16
1-5	11	21	9	4	7	52
6-10	9	8	5	3	3	28
11-17	22	25	18	16	11	92
Total	44	56	40	27	21	188

Data obtained from Organ Transplant and Procurement Network, December 13, 2013. http://optn.transplant.hrsa.gov (6).

infection that is active or resistant to treatment (10). Because outcomes for HLT are not great and surveillance is rigorous, relative or absolute contraindications to HLT may also be psychosocial issues such as severe depression, psychiatric disease or poor adherence to medical regimens (11). Previous thoracic surgery can complicate the technical aspects of the transplantation and so this may also need to be taken into consideration. Transplant from mechanical ventilation or mechanical support such as venous arterial (VA)/venous venous (VV) extracorporal membranous oxygenation (ECMO) is high risk. Our center will consider transplant from mechanical ventilation or VV ECMO. With complex congenital heart disease, significant aortopulmonary collaterals may develop with are a relative contraindication. Allosensitization increases the risk of rejection and graft failure post transplant and is a relative contraindication. Contraindications to isolated heart or DLT are similar.

Indications by year of age for HLT are summarized in *Table 1* (9). Congenital heart disease is more common as an indication in younger patients. PPHN is more common in older children. Eisenmenger's syndrome is most common in older children. A review of data from the Organ Procurement and Transplantation Network (OPTN) of the indications for heart lung transplant from 1/1/1988 through 7/31/2013 show that the number of HLT performed over the last 2 decades has remained stable. Since 1988, 188 HLT have been performed in individuals under the age of 18 at 33 centers in the United States. Of those, 48% were male, 47% blood group A, 41% blood group O, 77% Caucasian not of Hispanic origin. Nearly half (48.9%) of recipients were ages 11-17. In the same time period, 949 HLT were performed in adults 18 years of age and older. Pediatric HLT made up 16.5% of HLT performed in that era (9).

When the data from the OPTN is stratified by age groups, 16 (8.5%) were less than 1 year of age, 52 (27.7%) were ages 1-5, 28 (14.89%) were ages 6-10, and 92 (48.9%) of HLTs performed were in children ages 11-17 (9). In the youngest age group (less than 1 year), the three most common indications were congenital heart disease (31.25%), other (25%), and Eisenmenger's syndrome (12.5%). Only one recipient had a diagnosis of PPHN. One recipient had a diagnosis of pulmonary vascular disease. No HLTs have been reported in recipients less than 1 year of age since 2007. Children in the middle age groups (1-5 and 6-10) received HLT most commonly for PPHN and congenital heart disease. Children in the oldest age group (11-17) were also mostly transplanted for PPHN and congenital heart disease, but this is the age group in which Eisenmenger's syndrome was more common than the others. For data from ISHLT from 1982 to 2012 stratified by age groups, 21 (3%) were less than 1 year of age, 106 (15.6%) were ages 1-5, 127 (18.7%) were ages 6-10, and 425 (62.6%) of HLT performed were in children ages 11-17 (3).

When the OPTN data is stratified by era (*Table 2*), one notices that the overall number of HLTs has decreased in the most recent era [2008-2013] (9). Further dissection of the OPTN data would show that Eisenmenger's as an indication for HLT has decreased. Thirty recipients received HLT for Eisenmenger's syndrome up until 2002 and since then there have not been any HLTs performed for Eisenmenger's syndrome. PPHN and congenital heart disease have been common indications through all eras.

ISHLT data stratified by era also shows an overall decrease in the number of HLTs in the recent era, from a peak of 60 HLT in 1989 to <10 in 2011. Age distribution by era comparing 1982-1999 to 2000-2012 shows an increase in the percentage of patients who are ages 11-17 and <1 year of age at the time of transplant, and decrease in the percentage of patients who are ages 1-5 and 6-10 at the time of transplant. There is a decrease in the number of patients transplanted for cystic fibrosis and an increase in patients transplanted for pulmonary hypertension and congenital disease (3).

In 2012, there were two HLTs performed in North America for children less than 18 (12). Both recipients were

Table 3 Children's Hospital of Pittsburgh of UPMC HLT data

Diagnoses	Age <1	Age 1-5	Age 6-10	Age 11-17	Age 18-20	Total
All diagnoses	0	11	3	19	4	37
Eisenmenger syndrome	0	2	0	11	0	13
Heart re-transplant	0	0	0	0	0	0
Alpha 1	0	0	0	0	0	0
Lung re-transplant	0	0	0	2	0	2
Alveolar proteinosis	0	0	0	0	0	0
PPHN	0	5	2	1	0	8
PVR	0	0	0	0	0	0
RCM	0	0	0	0	0	0
Other	0	0	0	0	0	0
CHD	0	4	0	4	4	12
Congenital	0	0	0	0	0	0
CF	0	0	0	0	0	0
DCM	0	0	0	1	0	1
COPD	0	0	1	0	0	1

Internal Data as of December 15, 2013 (9). Alpha 1, Alpha 1 antitrypsin deficiency; PPHN, primary pulmonary hypertension; PVR, pulmonary vascular disease; RCM, restrictive cardiomyopathy; CHD, congenital heart disease; CF, cystic fibrosis; DCM, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease.

between 11-17 years of age. This is compared to 32 HLTs that were performed in adults in 2012. Even in the adults, the most common indications were PPHN (22%) and congenital heart disease (12%). To date for 2013, there have been 5 reported HLT. Two patients were age 1-5, 1 patient age 6-10, and 2 patients age 11-17. In the last 3 years, 6 centers have performed a total of 9 HLTs.

At our program, we have performed 37 HLT since 1988. Demographics with diagnoses by age are shown in *Table 3* (13). Forty-nine percent were male, 35% were blood group A, 30% blood group O, 92% were Caucasian not of Hispanic origin, 12 recipients (32%) were diagnosed with PPHN, 11 (30%) with congenital heart disease, and 9 (24%) with Eisenmenger's syndrome (13).

There have been case reports of unusual indications for HLT. Wuyts *et al.* described HLT in the setting of pulmonary artery dissection in patients with PPHN (14). Malignancy is typically considered a contraindication to transplantation, but cardiac tumors can be considered indications for transplantation. Talbot reported a case series of HLT for four patients with primary cardiac sarcomas involving the pulmonary artery and/or veins (15).

As discussed above, the indications for HLT have changed over the last 25 years (5). The primary indications in the USA remain PPHN, congenital heart disease, and Eisenmenger's syndrome. Cystic fibrosis historically is a common indication but has become less prevalent. While the indications for HLT have changed over time, the overall need for HLT and HT has also changed with the improved outcomes in pulmonary hypertension and congenital cardiac surgical centers allowing for correction of the cardiac defect and possibly only needing DLT if treatment of pulmonary hypertension is not sufficient. Diagnostics and therapies for pulmonary hypertension have improved which has allowed for earlier diagnosis and treatment.

Cardiac centers are offering palliative procedures to newborns with more complicated lesions with better outcomes than in prior decades (16). For example, survival for a first-stage palliation for hypoplastic left heart syndrome, a Norwood procedure, has improved compared with 15 years ago (17). In the 1990s, many centers offered HT or HLT as primary palliation for complex congenital heart disease, including hypoplastic left heart syndrome. Furthermore, patients with simple and complex congenital heart disease are being identified at a younger age (16). Fetal echocardiography has contributed to this as well as the introduction for universal pulse oximetry screening in the newborn period. Improved detection of congenital heart

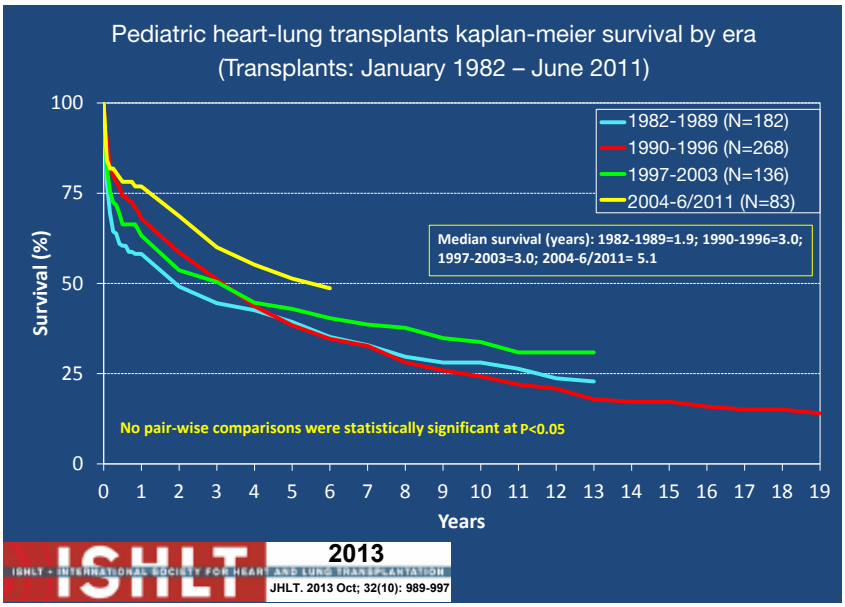

Figure 1 From the International Society for Heart and Lung Transplantation (ISHLT) data report (3). Pediatric HLT survival by era. Median survival in the most recent era is 5.1 years.

disease, and more importantly, improved surgical outcomes have decreased the risk of developing Eisenmenger's syndrome. Finally, single organ heart or double lung transplants are being performed in patients who would have received combined transplants in prior decades. This is partially as a result of better repair of congenital heart disease and ends up being helpful as there is often difficulty in obtaining heart-lung blocks

Despite all this, HLT will not become obsolete as centers are willing to perform more complex palliative operations for congenital heart disease. With advancement of medical treatment for pulmonary hypertension and surgical technique for palliation of congenital heart disease, transplant centers will need to offer HLT when medicine and surgery do not adequately treat the increasingly complex cases that are being cared for in heart and lung centers.

Outcomes

Outcomes for HLT are largely dependent upon the lung graft. Because DLT outcomes are relatively dismal in comparison to other solid organ transplants, the HLT outcomes can also be somewhat dismal. Five-year survival (Kaplan-Meier) for DLT is approximately 50% for both adults and children and remains significantly lower than survival for other solid organ transplants (3). As is shown in *Figure 1*, HLT survival is similar (1). A steep, early decline in survival that levels off at 1-3 months HLT reflects the impact of early events such as surgical complications, early graft failure, infection, and thromboembolism. Importantly, however, surgical outcomes have improved significantly over the last 20 years and so that steep, early decline in survival is no longer a major contributor to post-transplant mortality (also demonstrated in *Figure 1*). Unfortunately, the slow progressive decline that occurs after the early post-surgical period remains in both DLT and HLT. This is primarily due to chronic rejection of the lung. At our center, outcomes are similar to the national and international experience in that HT outcomes are better than those in DLT and HLT (13).

Surveillance to monitor the health of the heart-lung graft is of paramount importance when caring for children who have undergone transplantation. As previously indicated the lung graft is particularly susceptible to complications (especially rejection) and so the surveillance is mainly dictated by what is needed to assure good lung graft function. This monitoring consists of frequent evaluations. Examinations, lung function testing, evaluation of exercise capacity (6-minute walk testing), and surveillance bronchoscopy with transbronchial lung biopsies are the usual evaluations that occur to evaluate lung graft health. Specifically, since lung graft health is the limiting factor in

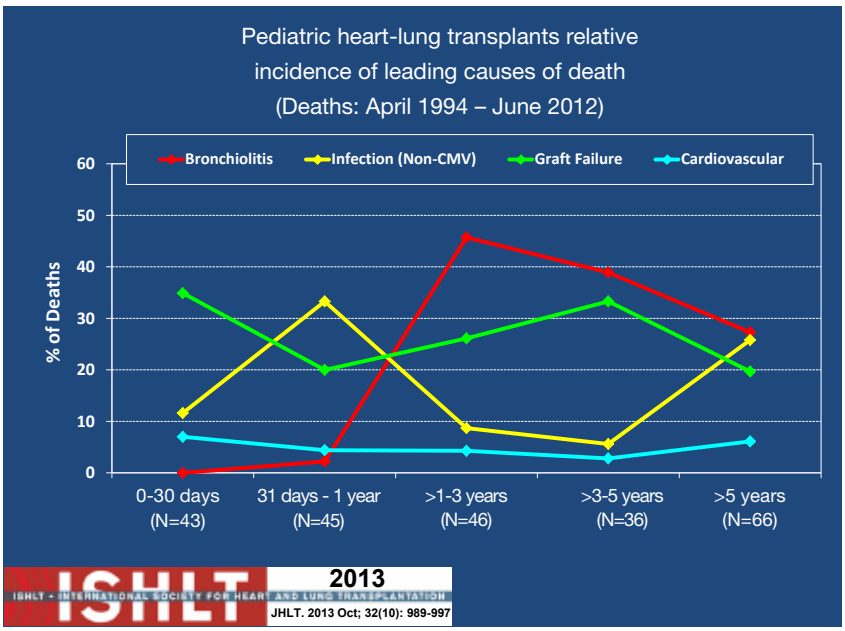

Figure 2 From the ISHLT data report (3). Pediatric HLT leading causes of death. Notice that lung allograft failure from Bronchiolitis is quite prevalent after 1 year whereas cardiovascular death is relatively rare.

HLT success, surveillance of the transplanted lungs with lung function, bronchoscopy, biopsy, and radiographs (often CT scanning) is important in the post-transplant period (18-23). Examinations, echocardiograms and evaluation of exercise capacity are also used to evaluate the heart graft health. Allograft rejection of the heart graft in HLT occurs less often than with HT alone (24). Therefore, rejection following HLT is most likely to occur in the lung graft. Surveillance endomyocardial biopsies are not indicated except in cases where heart rejection is suspected from cardiac studies and/or transbronchial lung biopsies are contraindicated. Monitoring for complications from immunosuppressive regimens include screening for systemic hypertension, renal insufficiency, hypercholesterolemia, diabetes, and osteoporosis (25). Finally, monitoring for conditions that are more prevalent in transplanted individuals such as post-transplant lymphoproliferative disease (PTLD) and malignancy are also of great importance (26).

The immunosuppressive regimen for any transplant that involves the lung is more intense because of the greater possibility for rejection of the lung graft. Because of this, complications that come from the immunosuppressive regimen and PTLD/malignancy need to be monitored for frequently and carefully. Because the monitoring is extensive and complications are common in the post-transplant period, many transplant experts counsel patients prior to transplant that having the procedure is like "trading one disease for another" (27). Furthermore, these outcomes have significant impact on the timing and decision to transplant as lung transplantation should occur when it is absolutely necessary in order to maximize the benefit of the transplant.

Bronchiolitis obliterans (BO) and infection have the greatest impact on long-term survival, and constant exposure of the lung to ambient air as well as aspiration of upper airway and/or refluxed gastroesophageal secretions are likely the major contributors to graft failure and death. BO is the pathologic mechanism by which chronic rejection occurs in the lung. Because of its significant prevalence and tendency to relentlessly progress, BO claims the lives of most individuals who survive the early post-operative period (28). This is the case for DLT and so this is why HLT survival primarily is dependent upon the lung graft. *Figure 2* illustrates the impact that BO has in mortality following HLT and the relative non-impact that cardiovascular disease has on mortality. One can also see the impact that infection has on mortality. Again, this is due to the intensity of the immunosuppressive regimen needed to preserve lung graft health and prevent rejection.

There are, however, two other factors that may affect survival of the HLT differently from DLT alone. These are

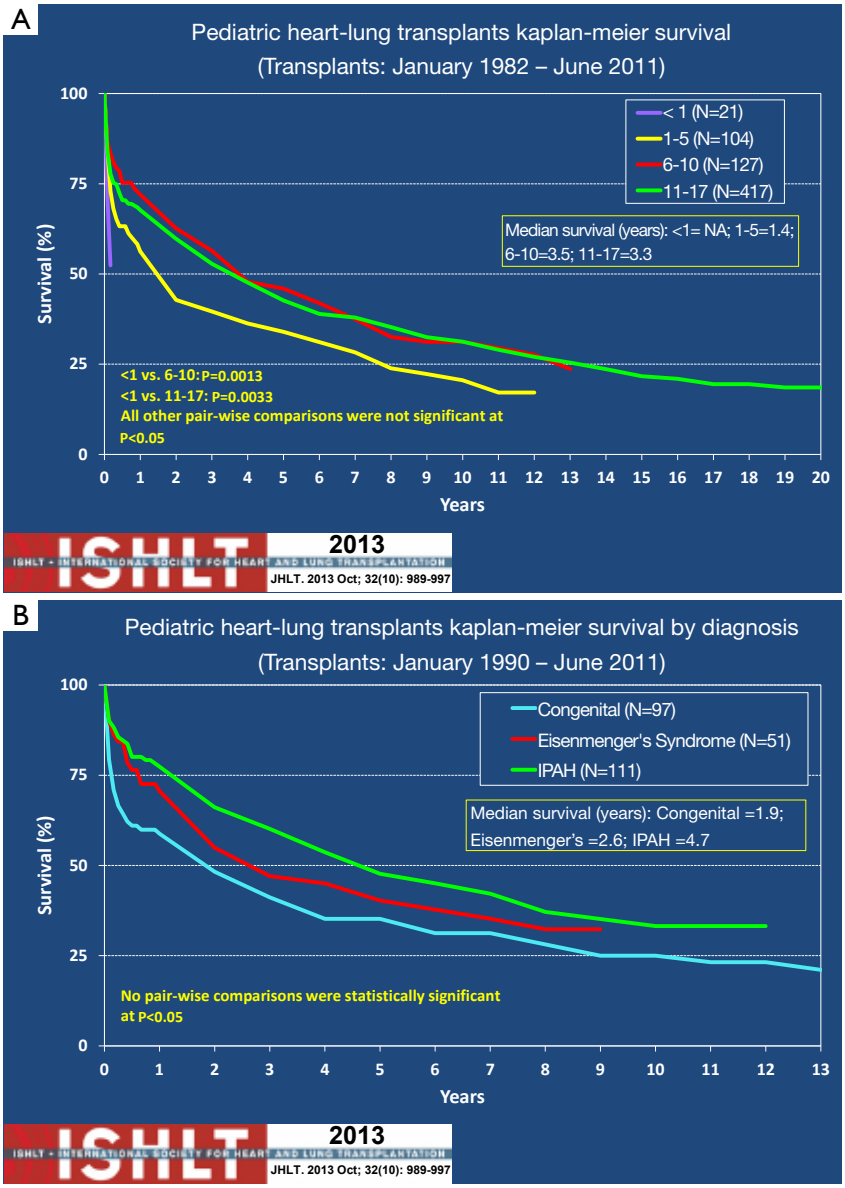

Figure 3 From the ISHLT data report (3). (A) Pediatric HLT survival by age shows that survival appears to be poorest in the age group <1; (B) although not statistically significant, survival appears to be better in those who undergo HLT for PPHN (IPAH, idiopathic pulmonary hypertension).

recipient age and the indication for transplantation. While minor in comparison to the effect BO and chronic lung rejection, these two factors do account for some discrepancy in survival among heart-lung recipients. Although debatable, *Figure 3A* shows that there is some concern that recipients less than 1 year of age have worse outcomes than older children who have undergone HLT (3,29). This is debatable because the number of HLTs that have occurred in children less than 1 year of age is very small. Outcomes for this age group could be highly dependent upon the experience of the transplant center as early outcomes are usually indicative of the success of the surgical procedure. Once beyond 2 years post-transplant infants with HLT have a similar risk of death as their older counterparts (3). The presence of Eisenmenger's syndrome or congenital heart disease portends a worse outcome post HLT than for PPHN (*Figure 3B*). This may be due to the likelihood that patients with PPHN have less chronic disease and may

have less deconditioning than those with Esienmenger's and congenital heart disease.

Despite the significant barriers that may occur and the relatively dismal outcomes expected from HLT, this therapy still remains an important therapy for children with end-stage heart and lung disease. And, for most, HLT can offer improved QOL (30). Heart and lung function also significantly improve. The majority of DLT and HLT recipients experience significant improvements in lung function and exercise tolerance (31-34). The greatest improvement in lung function usually occurs in the first three months after DLT/HLT and slowly reaches a plateau at about one year, barring any concurrent significant complications that affect lung function (31). Normalization of pulmonary pressures, ventricular function and cardiac output are expected for patients who receive a HLT for pulmonary hypertension and cardiac disease.

Exercise tolerance improves greatly and allows most recipients to perform activities of daily living without limitation or need for supplemental oxygen or other supportive therapy. Over 80% of survivors at 1, 3, and 5 years post-transplant have no activity limitations (3). However, cardiopulmonary exercise testing reveals that maximum oxygen consumption is limited to 50-60% predicted at peak exercise (34). Deconditioning and a possible myopathy that is linked to the immunosuppressant regimen or other factors likely accounts for this limited exercise capacity, because cardiopulmonary reserve appears to be maintained. Recipients of heart, liver and kidney transplants have similar limitations on cardiopulmonary exercise, suggesting that factors other than graft function may account for the subnormal maximum oxygen consumption at peak exercise. In recipients of HLT versus DLT who were stable and otherwise well, there does not appear to be a difference in exercise capacity indicating that a healthy lung graft post-transplant does not appear to be the limiting organ. It is the cardiovascular response that appears to limit oxygen consumption at peak exercise (34).

QOL evaluations demonstrate that this procedure is perceived to be worthwhile to recipients. Most patients who have undergone transplant have been found to be happy with their decision to undergo the procedure (30). Interestingly, recent data have shown that 1-year QOL analysis for lung transplant recipients demonstrates a positive outcome for physical but not psychologic well-being. This demonstrates that transplant can confer physiologic improvements but the patient continues to have considerable medical burden in the post-transplant period with medical therapies, surveillance and fear of complications (35).

In children who have undergone thoracic transplantation, cognitive, academic and behavioral concerns arise after transplantation (36). This underscores the importance of psychosocial evaluation and counseling in the pre- and post-transplant period as this treatment can have effects on the patient and family. Despite these concerns about complications and outcomes, HLT can be an important therapy for those with end-stage heart and lung disease and success is determined by meticulous evaluation and surveillance.

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References

1. Reitz BA. The first successful combined heart-lung transplantation. J Thorac Cardiovasc Surg 2011;141:867-9.
2. Orens JB, Shearon TH, Freudenberger RS, et al. Thoracic organ transplantation in the United States, 1995-2004. Am J Transplant 2006;6:1188-97.
3. Benden C, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Lung and Heart-Lung Transplantation Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:989-97.
4. Kotsimbos T, Williams TJ, Anderson GP. Update on lung transplantation: programmes, patients and prospects. Eur Respir Rev 2012;21:271-305.
5. Franke U, Wiebe K, Harringer W, et al. Ten years experience with lung and heart-lung transplantation in primary and secondary pulmonary hypertension. Eur J Cardiothorac Surg 2000;18:447-52.
6. Goerler H, Simon A, Gohrbandt B, et al. Heart-lung and lung transplantation in grown-up congenital heart disease: long-term single centre experience. Eur J Cardiothorac Surg 2007;32:926-31.
7. Goldstein BS, Sweet SC, Mao J, et al. Lung transplantation in children with idiopathic pulmonary arterial hypertension: an 18-year experience. J Heart Lung Transplant 2011;30:1148-52.
8. Schwebel C, Pin I, Barnoud D, et al. Prevalence and consequences of nutritional depletion in lung transplant candidates. Eur Respir J 2000;16:1050-5.
9. Data from the Organ Procurement and Transplantation Network (OPTN). As of December 13, 2013. Available

online: http://optn.transplant.hrsa.gov
10. Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;115:658-76.
11. Dobbels F, Vanhaecke J, Desmyttere A, et al. Prevalence and correlates of self-reported pretransplant nonadherence with medication in heart, liver, and lung transplant candidates. Transplantation 2005;79:1588-95.
12. International Society for Heart and Lung Transplantation (ISHLT) Registry Quarterly Reports for Heart/Lung in North America. As of December 4, 2013.
13. Children's Hospital of Pittsburgh of UPMC, Heart and Lung Transplant. Internal data as of December 15, 2013.
14. Wuyts WA, Herijgers P, Budts W, et al. Extensive dissection of the pulmonary artery treated with combined heart-lung transplantation. J Thorac Cardiovasc Surg 2006;132:205-6.
15. Talbot SM, Taub RN, Keohan ML, et al. Combined heart and lung transplantation for unresectable primary cardiac sarcoma. J Thorac Cardiovasc Surg 2002;124:1145-8.
16. van der Bom T, Zomer AC, Zwinderman AH, et al. The changing epidemiology of congenital heart disease. Nat Rev Cardiol 2011;8:50-60.
17. Feinstein JA, Benson DW, Dubin AM, et al. Hypoplastic left heart syndrome: current considerations and expectations. J Am Coll Cardiol 2012;59:S1-42.
18. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002;21:297-310.
19. Trulock EP, Ettinger NA, Brunt EM, et al. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. Chest 1992;102:1049-54.
20. Aboyoun CL, Tamm M, Chhajed PN, et al. Diagnostic value of follow-up transbronchial lung biopsy after lung rejection. Am J Respir Crit Care Med 2001;164:460-3.
21. Chakinala MM, Ritter J, Gage BF, et al. Yield of surveillance bronchoscopy for acute rejection and lymphocytic bronchitis/bronchiolitis after lung transplantation. J Heart Lung Transplant 2004;23:1396-404.
22. Bankier AA, Van Muylem A, Knoop C, et al. Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. Radiology 2001;218:533-9.
23. Lee ES, Gotway MB, Reddy GP, et al. Early bronchiolitis obliterans following lung transplantation: accuracy of expiratory thin-section CT for diagnosis. Radiology 2000;216:472-7.
24. Hayes D Jr, Galantowicz M, Hoffman TM. Combined heart-lung transplantation: a perspective on the past and the future. Pediatr Cardiol 2013;34:207-12.
25. Spira A, Gutierrez C, Chaparro C, et al. Osteoporosis and lung transplantation: a prospective study. Chest 2000;117:476-81.
26. Leblond V, Sutton L, Dorent R, et al. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. J Clin Oncol 1995;13:961-8.
27. Kurland G, Orenstein DM. Lung transplantation and cystic fibrosis: the psychosocial toll. Pediatrics 2001;107:1419-20.
28. Scott JP, Higenbottam TW, Sharples L, et al. Risk factors for obliterative bronchiolitis in heart-lung transplant recipients. Transplantation 1991;51:813-7.
29. Deuse T, Sista R, Weill D, et al. Review of heart-lung transplantation at Stanford. Ann Thorac Surg 2010;90:329-37.
30. Choong CK, Meyers BF. Quality of life after lung transplantation. Thorac Surg Clin 2004;14:385-407.
31. Egan TM, Detterbeck FC, Mill MR, et al. Improved results of lung transplantation for patients with cystic fibrosis. J Thorac Cardiovasc Surg 1995;109:224-34; discussion 234-5.
32. Levy RD, Ernst P, Levine SM, et al. Exercise performance after lung transplantation. J Heart Lung Transplant 1993;12:27-33.
33. Williams TJ, Patterson GA, McClean PA, et al. Maximal exercise testing in single and double lung transplant recipients. Am Rev Respir Dis 1992;145:101-5.
34. Levy RD, Ernst P, Levine SM, et al. Exercise performance after lung transplantation. J Heart Lung Transplant 1993;12:27-33.
35. Finlen Copeland CA, Vock DM, Pieper K, et al. Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. Chest 2013;143:744-50.
36. Brosig C, Hintermeyer M, Zlotocha J, et al. An exploratory study of the cognitive, academic, and behavioral functioning of pediatric cardiothoracic transplant recipients. Prog Transplant 2006;16:38-45.

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Brief Report

Heart-lung transplantation: adult indications and outcomes

Yoshiya Toyoda[1], Yasuhiro Toyoda[2]

[1]Temple University, USA; [2]University of Pittsburgh, USA

Correspondence to: Yoshiya Toyoda, MD, PhD. Professor of Surgery, Temple University School of Medicine, 3401 N. Broad Street, Suite 301, Zone C, Philadelphia, PA 19140, USA. Email: Yoshiya.Toyoda@tuhs.temple.edu.

Abstract: Combined heart-lung transplantation remains the only definitive therapy for patients who have both end-stage heart failure and end-stage lung failure. The most common indication is congenital heart disease (CHD) and the proportion is increasing for acquired heart disease concomitant with pulmonary hypertension and/or intrinsic lung diseases. Previously, idiopathic pulmonary hypertension was the most common indication. However, it has been shown that right ventricular failure can be reversed after double lung transplantation. Therefore, patients with idiopathic pulmonary arterial hypertension (IPAH) should not undergo combined heart-lung transplantation unless left ventricular dysfunction co-exists. The ISHLT registry data shows survival after heart-lung transplantation is improving, but still its survival rates are 71% at 3 months, 63% at 1 year, 44% at 5 years and 31% at 10 years. With appropriate patient selection and surgical expertise, these outcomes should improve further.

Keywords: Heart-lung transplantation; idiopathic pulmonary arterial hypertension (IPAH), congenital heart disease (CHD); extracorporeal membrane oxygenation; ventricular assist device

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Adult indications

The international society of heart and lung transplantation (ISHLT) registry data shows idiopathic pulmonary arterial hypertension (IPAH) was the most common indication followed by congenital heart disease (CHD) and cystic fibrosis (CF) in 1982-1991 (n=959) (1). The data from the most recent period from 2002 to June of 2012 (n=829), however, shows that CHD became the most common indication followed by IPAH. The proportion decreased for CF and increased for acquired heart disease.

Decrease of the proportion for IPAH is in agreement with our recommendation. We have shown an excellent outcome with double lung transplant and combined heart-lung transplantation for patients with IPAH when indication for HLTx is inotropic dependency for right ventricular support and/or concomitant left ventricular dysfunction (2). However, further study is necessary to determine whether double lung transplant is sufficient even for patients with inotropic dependency for right ventricular failure.

We have experienced 17 heart-lung transplants from 2005 to 2012 for the indications shown in the *Figure 1*.

In our experience, CHD was the most common indication for HLTx, including transposition of the great arteries s/p Mustard operation with systemic ventricular failure and pulmonary hypertension, Shone's syndrome with pulmonary hypertension, Eisenmenger's syndrome s/p ventricular and/or atrial septal defect repair, polysplenia syndrome, etc. Because of previous multiple surgeries and potential sensitization due to multiple blood transfusion and use of homograft, complex CHD is a challenging indication and only experienced surgeons who are familiar with CHD should perform the surgery.

Case presentation 1

A 27-year-old man with Shone's syndrome had repair of coarctation of the aorta and mitral valve replacement three times previously. At the time of HLTx, he had been on mechanical ventilation with FiO_2 70% and inhaled nitric oxide at 40 ppm for 5 days and he was on 10 mcg/kg/min of dopamine and 0.1 mcg/kg/min of norepinephrine

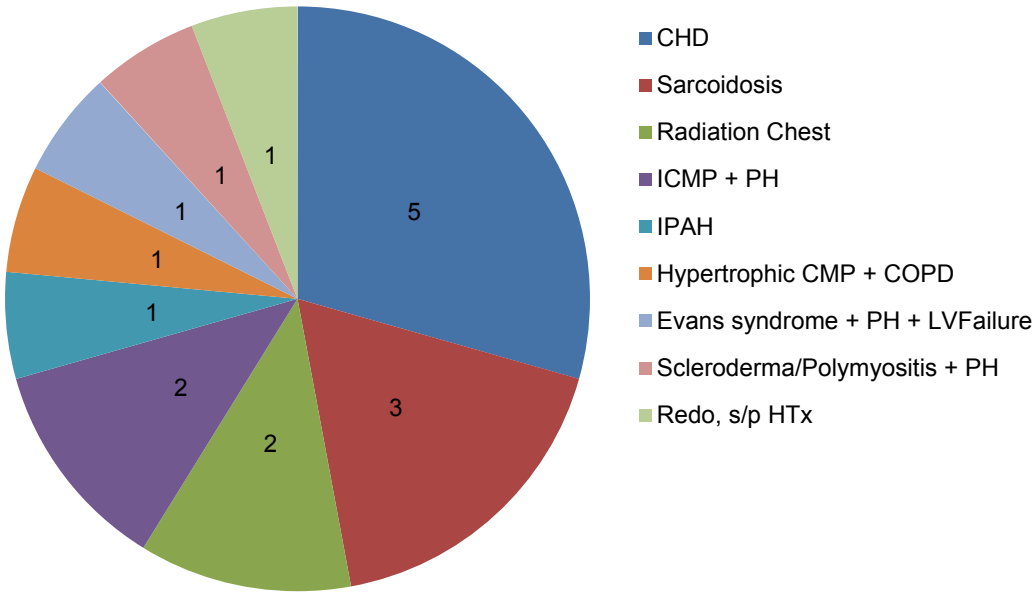

Figure 1 Indications for heart-lung transplantation (n=17, YT, 2005-12). CHD, congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension.

to maintain his blood pressure. He had kidney failure on continuous veno-venous hemodialysis. Despite his critically ill condition, he continued to be listed and underwent a combined heart-lung transplantation utilizing organs from a 40-year-old female donor. Total ischemic time was 274 minutes, warm ischemic time (organ in the chest till reperfusion) 42 minutes, and cardiopulmonary bypass time 336 minutes. Postoperatively, due to preoperative low output, he required bilateral below-knee amputation due to ischemic legs. His hospital stay was 151 days. However, the patient is now doing well more than 4 years postoperatively with normal heart, and lung functions. We believe this case suggests the limit for a successful outcome after HLTx.

We have experienced three sarcoidosis. Pulmonary and cardiac involvements were common. As in other diseases, careful assessment of other organ function is important. In fact, we have performed a combined heart, lung and liver transplantation for a patient who had congestive liver cirrhosis in addition to end-stage heart and lung diseases as shown below.

Case presentation 2

A 49-year-old man had pulmonary and cardiac sarcoidosis with severe pulmonary hypertension and liver cirrhosis on Mirinone 0.375 mcg/kg/min. A combined heart-lung-liver transplantation was performed utilizing organs from an 18-year-old male donor. The total ischemic time was 164 minutes and cardiopulmonary bypass time was 264 minutes. The patient is doing well with normal heart, lung and liver functions more than 5 years postoperatively. Thus, sarcoidosis seems a good indication for HLTx and perhaps liver or kidney transplant concomitant with HLTx.

As a unique group of patients, we have experienced two patients who had extensive, mantle radiation to the chest for Hodgkin lymphoma. Both patients had pleurodesis and had extensive, severe adhesions. In our limited experience, radiation chest may have to be considered as a relative contraindication for HLTx.

As the ISHLT registry data indicated, acquired heart disease is increasing as an indication for HLTx. We had two ischemic cardiomyopathy and pulmonary hypertension and one hypertrophic cardiomyopathy and COPD. These three patients were on left or bi-ventricular assist devices (VAD) preoperatively. As more and more patients with end-stage heart failure are managed with VADs as a bridge-to-heart transplantation, we need to carefully monitor their lung status including pulmonary hypertension. Especially when a patient is on RVAD, chronic thromboembolic pulmonary hypertension can occur due to thrombus formed in the RVAD while waiting for a heart transplant. In such situation, the patient may have to be placed in heart-lung transplant list rather than heart transplant only. Thus,

pulmonary hypertension and/or end-stage lung disease in the setting of predominant left and/or biventricular failure can be a good indication for HLTx.

Case presentation 3

A 47-year-old man who had bi-ventricular assist device for his hypertrophic cardiomyopathy. He was found to have severe pulmonary hypertension and Child B, MELD 12, liver cirrhosis. He successfully underwent a HLTx from an 39-year-old male donor. Total ischemic time was 192 minutes, warm ischemic time (organ in the chest till reperfusion) 36 minutes, and cardiopulmonary bypass time 185 minutes.

On the other hand, only 1 patient had IPAH (6%) as an indication for HLTx in our experience. During the same time period, we have performed 5 double lung transplants for IPAH. In patients with pulmonary hypertension and right ventricular failure, we need to determine if the right ventricle is sick enough to warrant HLTx. Based on our experience, both acute and chronic right ventricular failure due to severe pulmonary hypertension and hypoxia, which requires inotropic support and/or even veno-arterial extracorporeal membrane oxygenation, can be reversed after double lung transplantation by normalizing the pulmonary vascular resistance. Therefore, virtually all patients with IPAH should receive double lung transplantation, and HLTx is not necessary as far as the left ventricle is normal. Left ventricular dysfunction in the setting of pulmonary hypertension and right ventricular failure, can be the reason for HLTx. The question is what degree of left ventricular dysfunction necessitates HLTx. In our experience, LVEF 30-35% is still sufficient for double lung transplantation alone if the right heart catheterization shows good cardiac index (e.g., >2.2 L/min/m^2) and low filling pressures (e.g., PCWP and/or LVEDP ≤15 mmHg).

Patients who have end-stage lung disease with repairable cardiac diseases can be treated by lung transplantation and concomitant cardiac surgery such as coronary artery bypass surgery, valve repair/replacement, repair of CHDs, etc.

Regarding recipient age limit, in our opinion, there should not be a rigid chronological age limit. The ISHLT registry data also suggests the age limit is increasing. Almost 5% of HLTx recipient were age 60 and older and some were 65 and older from 2006 to 2012 (1). If a patient has good other organ functions and the physiological age seems reasonable, we would consider up to 70 years old or so for HLTx. Regarding donor age limit, we would consider up to around 60 years old in agreement with the ISHLT registry data.

Adult outcomes

The ISHLT registry data shows survival rates of 71% at 3 months, 63% at 1 year, 44% at 5 years and 31% at 10 years. Recipients who survived the first year had a median survival of 10.0 years. A multivariable analysis of risk factors for 1-year mortality showed IPAH as favorable diagnosis [hazard risk (HR): 0.78, 95% confidence interval (CI): 0.63-0.96, P=0.0171] and donor age as a significant independent predictor for 1-year mortality, although it did not demonstrate recipient age as a predictor.

Variables influencing survival in heart-lung recipients are not well established. We have analyzed 542 adult patients who received heart-lung transplantation from 1995 to 2011 in the UNOS database (3). Although the use of ECMO as a bridge to lung transplantation is an accepted therapy for patients with end-stage lung disease (4), the role of ECMO as a bridge to combined adult HLT has only been described in case reports (5,6). Our multivariate analysis demonstrated that preoperative use of extracorporeal membrane oxygenation (ECMO, HR: 3.820, 95% CI: 1.600 to 9.112, P=0.003) and mechanical ventilator (HR: 2.011, 95% CI: 1.069 to 3.784, P=0.030) is a risk factor for mortality and recipient female gender (HR: 0.754, 95% CI: 0.570 to 0.998, P=0.048) is associated with better survival (3).

Mechanical circulatory support bridge-to-HLTx

Of the 17 patients in our experience, 5 patients were supported with mechanical circulatory support at the time of HLTx. We have successfully performed HLTx for 2 patients who were on veno-arterial ECMO preoperatively. Two other patients were on bi-ventricular assist deivces and one on left ventricular assist device. All patients survived HLTx surgery with 100% survival at 30, 90, 180 and 300 days with 1-year survival rate of 80%. Good outcomes can be achieved even for patients who required mechanical circulatory support including ECMO preoperatively.

Case presentation 4

A 41-year-old female who has chronic lung infections due to Evans syndrome and hypogammaglobulinemia developed severe pulmonary hypertension, right ventricular failure and hypoxia. She was listed for double lung transplantation, however, she was admitted with worsening shortness of breath and lower extremity edema. She was intubated and mechanically ventilated with FiO_2 100%, PEEP 15 cm H_2O

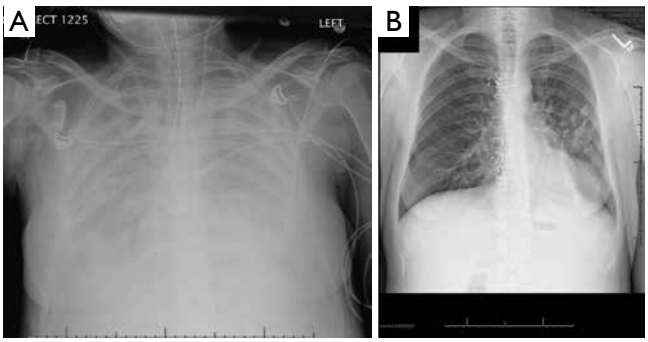

Figure 2 (A) Preoperative Chest X-ray; (B) Postoperative Chest X-ray.

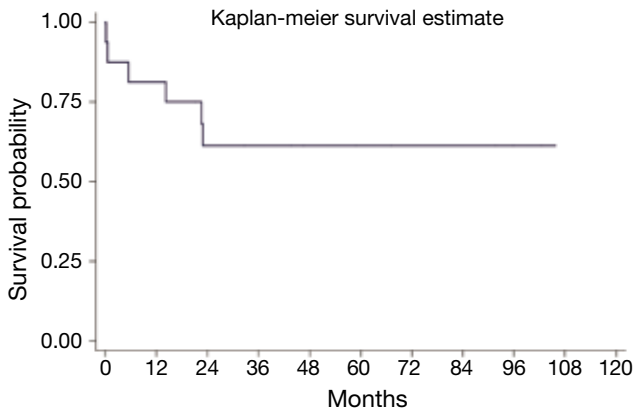

Figure 3 Survival after HLTx (n=17, YT, 2005-12).

and inhaled nitric oxide, and required inotopes for her right ventricular failure (*Figure 2A*). She developed cardiac arrest in the intensive care unit and was placed on veno-arterial ECMO. Her echo showed LVEF 10%. She was then listed for heart-lung transplant. After ECMO support for 8 days, heart-lung transplantation was performed using the organs from a 27-year-old male donor. The ischemic time was 136 minutes, the warm ischemic time 43 minutes and cardiopulmonary bypass time 215 minutes. Her ECMO was weaned in the OR. She was extubated on postoperative day #1 (*Figure 2B*). The ICU stay was 5 days. She was discharged home on postoperative day #32. Her right heart catheterization showed RA 2, PAP 32/9 (21), PCWP 10, and cardiac index 4.35 L/min/m^2. Her PFT showed FVC 2.89 L (78%) and FEV1 2.21 L (74%). She is doing well as of 1 year postoperatively. This case suggests that preoperative ECMO should not be an absolute contraindication, and with appropriate expertise, a good outcome can be achieved.

As mentioned above, we have experienced three sarcoidosis patients who had both left ventricular dysfunction and end-stage lung disease with severe pulmonary hypertension. A patient even had liver involvement with liver failure requiring a combined heart-lung and liver transplantation. All three patients are surviving 2-5 years (100% survival rate at 1 and 5 years). Sarcoidosis is a good indication for HLTx if patients have both heart and lung failure, but we need to assess other organ dysfunctions for additional organ transplants. On the other hand, both patients who had prior mantle radiation to the chest did not survive for 1 year (0% 1-year survival).

Overall, 3-month, 1-year and 5-year survival rates were 88%, 81% and 61%, respectively (*Figure 3*). These results are favorable when compared to the ISHLT registry data which showed 71% at 3 months, 63% at 1 year and 44% at 5 years although our patient cohort seemed to be higher-risk patients because No. 1: only 1 patient had IPAH (best indication for better outcomes), No. 2: 5 patients (29%) were on mechanical circulatory support including 2 ECMOs and 3 VADs at the time of HLTx, No.3: 2 patients had radiation chest. No. 4: 4 patients were on mechanical ventilation and in profound cardiogenic shock.

To achieve the best possible outcomes, surgeons need to do the best possible job in the OR. First, surgeons need to achieve good hemostasis after explantation of the heart-lung block from the recipient chest before starting implantation. Second, tracheal anastomosis should be done by making the donor trachea as short as possible. The surrounding tissue of the recipient and donor trachea should be preserved as much as possible and it should be used to cover the tracheal anastomosis. Third, the aortic anastomosis should be done immediately after the tracheal anastomosis, and the heart should be reperfused immediately after the aortic anastomosis to minimize the total and warm ischemic time. Fourth, preservation/protection and management of the heart and lung are important.

In summary, as the last resort for patients with end-stage heart and lung failure, combined heart-lung transplantation remains an excellent, viable therapy, and excellent outcomes can be achieved when the patient selection is appropriate for surgical expertise.

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References

1. Yusen RD, Christie JD, Edwards LB, et al. The Registry

of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
2. Toyoda Y, Thacker J, Santos R, et al. Long-term outcome of lung and heart-lung transplantation for idiopathic pulmonary arterial hypertension. Ann Thorac Surg 2008;86:1116-22.
3. Jayarajan SN, Taghavi S, Komaroff E, et al. Impact of extracorporeal membrane oxygenation or mechanical ventilation as bridge to combined heart-lung transplantation on short-term and long-term survival. Transplantation 2014;97:111-5.
4. Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg 2013;145:1065-70; discussion 1070-1.
5. Gregoric ID, Chandra D, Myers TJ, et al. Extracorporeal membrane oxygenation as a bridge to emergency heart-lung transplantation in a patient with idiopathic pulmonary arterial hypertension. J Heart Lung Transplant 2008;27:466-8.
6. Strueber M, Hoeper MM, Fischer S, et al. Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. Am J Transplant 2009;9:853-7.

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Review Article

Preservation solutions for cardiac and pulmonary donor grafts: a review of the current literature

Nicholas Latchana[1], Joshua R. Peck[2], Bryan Whitson[3,4], Sylvester M. Black[1,4]

[1]Department of Surgery, Division of Transplantation, [2]Department of Internal Medicine, [3]Department of Surgery, Division of Cardiac Surgery, [4]The Collaboration for Organ Perfusion, Protection, Engineering and Regeneration (COPPER) Laboratory, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Correspondence to: Sylvester M. Black, MD, PhD. Department of Surgery, Division of Transplantation, The Ohio State University Wexner Medical Center, 395 W 12th Avenue, Columbus, Ohio 43210, USA. Email: Sylvester.Black@osumc.edu.

Abstract: Hypothermic preservation of donor grafts is imperative to ameliorate ischemia related cellular damage prior to organ transplantation. Numerous solutions are in existence with widespread variability among transplant centers as to a consensus regarding the optimal preservation solution. Here, we present a concise review of pertinent preservation studies involving cardiac and pulmonary allografts in an attempt to minimize the variability among institutions and potentially improve graft and patient survival. A biochemical comparison of common preservation solutions was undertaken with an emphasis on Euro Collins (EC), University of Wisconsin (UW), histidine-tryptophan-ketoglutarate (HTK), Celsior (CEL), Perfadex (PER), Papworth, and Plegisol. An appraisal of the literature ensued containing the aforementioned preservation solutions in the setting of cardiac and pulmonary transplantation. Available evidence supports UW solution as the preservation solution of choice for cardiac transplants with encouraging outcomes relative to notable contenders such as CEL. Despite its success in the setting of cardiac transplantation, its use in pulmonary transplantation remains suboptimal and improved outcomes may be seen with PER. Together, we suggest, based on the literature that the use of UW solution and PER for cardiac and pulmonary transplants, respectively may improve transplant outcomes such as graft and patient survival.

Keywords: Preservation; donor; cardiac; pulmonary; transplantation

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Introduction

Despite many of the advances within the realm of transplantation, graft survival remains imperfect. Optimal preservation of the graft is an important determinant of graft survival and patient outcomes. Considerable attention is given to the *ex vivo* period as this segment represents a vulnerable timeframe whereby organs are susceptible to ongoing cellular damage that is further compounded by reperfusion injury upon re-anastomosis. Hypothermia is utilized to decrease the metabolic activity of donor organs during the *ex vivo* period. Decrease donor organ temperature from 37 to 4 ℃ results in a 12 fold decrease in the metabolic demand (1). However, hypothermia alone is unable to abolish all cellular damage as metabolism persists at approximately 5-10% of normal. In addition, hypothermia can lead to Na^+/K^+ ATPase alterations, ATP depletion, dysregulation of Ca^{2+} homeostasis, mitochondrial perturbations, xanthine oxidase accumulation, and increased levels of reactive oxygen species (ROS) which may have deleterious effects on cellular viability (2). Therefore, preservation solutions have been implemented in conjunction with hypothermia for additional cellular protection. Numerous solutions are commercially available while others remain institutionally derived.

There is continued uncertainty among clinicians regarding the most optimal preservation solution as evidenced by Demmy *et al.* who revealed the use of 167 different

solutions among United Network for Organ Sharing (UNOS) cardiac transplant centers (3). It is clear that investigation concerning the optimal preservation solution is necessary to reduce such widespread variability and potentially improve graft outcomes. As such, we sought to review the pertinent clinical studies available in an attempt to identify characteristics of an ideal preservation solution for both cardiac and pulmonary grafts with the intention of ultimately minimizing graft dysfunction and improving patient outcomes.

Classification of preservation solutions

Preservation solutions

Euro Collins (EC) solution was designed in the 1960s and considered the preservation solution of choice for over 15 years until organ perseveration was revolutionized by the introduction of University of Wisconsin (UW) solution in 1988 (4). However, the high molecular weight compounds within UW such as hydroxyethyl starch (HES) resulted in a highly viscous solution that was implicated in part, to organ dysfunction thereby, supporting the development of less vicious alternatives including Celsior (CEL) and histidine-tryptophan-ketoglutarate (HTK) (5).

Many targeted approaches to cardiac organ preservation have been attempted including Plegisol which arose from the initial St. Thomas solution used for cardioplegia, albeit with slight modifications including the addition of a buffering system (6). In contrast to the aforementioned acellular approaches, Papworth solution was centered on the inclusion of donor blood in its composition (7). The different metabolic demand and physiology of the lung supported the construction of pulmonary specific solutions including Perfadex (PER) which still remains confined for sole use in pulmonary transplantations by the Federal Drug Administration (FDA) in the United States.

Preservation solutions are composed of multiple elements, each with their own advantages and disadvantages (*Table 1*). We will highlight a common classification scheme for EC, UW, HTK, CEL, PER, Papworth, and Plegisol according to respective molecular properties.

Intracellular/extracellular

Preservation solutions can be broadly classified into intracellular and extracellular solutions based upon the potassium and sodium concentrations. Intracellular solutions closely recapitulate the high potassium/low sodium conditions present within the cellular milieu to minimize potential concentration gradients across the plasma membrane that could favor potassium efflux. UW and EC are popular intracellular solutions, however the perceived risk of hyperkalemia induced pulmonary vasoconstriction favored the design of extracellular (low potassium) solutions such as HTK, CEL, PER, Papworth, and Plegisol (10). Over time, intracellular and extracellular solutions were shown to be equivalent (10).

Impermeant/colloid

Hypothermia causes dysregulation of the Na^+/K^+ pumps in the cellular membrane resulting in cellular edema through sodium and water influx into the cell (12). The addition of an impermeant or colloid creates an osmotic force that preferentially promotes water retention in the extracellular compartment to counteract this effect. EC contains a high concentration of glucose that was intended to act as impermeable barrier. However, glucose is suboptimal as enzymatic cleavage occurs resulting in substrate diffusion into the cell and subsequent cellular edema (2). The development of newer solutions containing alternate impermeants/colloids led to superior protection against cellular swelling. UW contains lactobionate and the trisaccharide impermeant raffinose as well as the synthetic colloid HES (Roskott *et al.*). HTK, CEL, and Papworth rely on mannitol to combat tissue edema (9). In addition to mannitol, lactobionate and albumin are included in CEL and Papworth, respectively for further protection (9,11).

Buffer

Many of the commercial preservation solutions contain a buffer to combat the effects of metabolic acidosis that result from the shift of aerobic to anaerobic metabolism during periods of ischemia. UW, PER, and EC utilize phosphate buffers whereas, HTK and CEL are comprised of histidine buffering systems to prevent cellular damage (8,9). Bicarbonate is an effective buffer and used in EC and Plegisol (6,8).

Antioxidants

ROS are an inevitable consequence of tissue ischemia during the *ex vivo* period and can lead to significant cellular damage. UW counteracts ROS with a combination of allopurinol to inhibit the formation xanthine oxidase and glutathione which can act as a reducing agent (9). Glutathione is also the mainstay of antioxidant activity in CEL (9). HTK's antioxidant properties are attributed to tryptophan which is a functional electron donor (10).

Table 1 Comparison of select perfusate solutions

	EC	UW	HTK	CEL	PER	Papworth	Plegisol
Study	Aziz (8)	Roskott (9)	Roskott (9), 't Hart (10)	Roskott (9), 't Hart (10)	Aziz (8)	Marasco (11), Divisi (7)	Chambers (6)
IC/EX	IC	IC	EX	EX	EX	EX	EX
Na^+	10	25	15	100	138	115	120
K^+	115	120	10	15	6	3	16
Impermeant/ colloid	Glucose	LactoB, raffinose, HES	Mannitol	LactoB, mannitol	Dextran	Mannitol, albumin	–
Buffer	Phos, bicarb	Phos	Histidine	Histidine	Phos	–	Bicarb
Antioxidant	–	AlloP, GSH	Trp, mannitol	GSH, mannitol	–	Mannitol	–
Osmolarity (mOsm/L)	375	330	310	320	292	440	320
Ca^{2+}	–	–	0.02	0.25		Und	1.2
Mg^{2+}	–	5	4	13	0.8	–	16
Cl^-	15	20	32	–	142	Und	160
Glucose	180	–	–	–	5	–	–
Others			α-KG		SO_4^{2-} 0.8, dextran 40 g/L	Donor blood heparin	–

All units expressed in mmol/L unless otherwise indicated. Abbreviations: IC, intracellular; EX, extracellular; EC, Euro Collins; UW, University of Wisconsin; HTK, histidine-tryptophan-ketoglutarate; CEL, Celsior; PER, Perfadex; Und, undetermined; LactoB, lactobionate; HES, hydroxyethyl starch; Phos, phosphate; Bicarb, bicarbonate; GSH, glutathione; AlloP, allopurinol; Trp, tryptophan; α-KG, ketoglutarate.

Moreover, mannitol has been suggested to have antioxidant properties which may confer a benefit to CEL, HTK, and Papworth (10).

Heart transplantation

Although ischemia times as long as 13 hours have been reported for heart transplants, cold ischemia times are usually limited to less than 6 hours (13,14). CEL was initially a favorable extracellular preservation solution for heart transplants with several studies supporting its use (*Table 2*). A prospective study containing 70 patients revealed a safe role for CEL as a preservation solution in the setting of heart transplants with a 30-day survival of 91.4% and acute graft failure rate of 10% (15). This was supported by De Santo *et al*. who found an in-hospital mortality rate of 8% and 1 year mortality rate of 12% in 200 patients that received CEL (16). Interestingly, upon stratification into low and high risk grafts in that study, there was no difference in mortality or graft failure suggesting a potential safe role for the use of CEL even in the setting of prolonged ischemia (>180 minutes) (16).

Given the suggested beneficial role of CEL, many comparison trials were performed. An evaluation of 48 patients (24 HTK and CEL 24) suggested a beneficial role for CEL as only one case of graft failure was observed in the CEL arm compared to two in the HTK group. However, the results of this study were preliminary and the low number of patients made it difficult to derive any meaningful conclusions (17). Vega *et al*. (18) evaluated 131 patients with the use of CEL (n=64) to several other solutions (n=67) including: UW, Plegisol, Stanford solution, PlasmaLyte A, Carmichael solution, Roe, lactate ringers, and normal saline. There was no difference in the mortality rate at 30 days (CEL 94% *vs*. others 88%) or graft failure rate at 30 days (CEL 6.3, Cntrl 13.4%; P not listed) (18). Although comparisons of CEL to the use of a specific solution could not be made given the variety of controls in this study, it did once again demonstrate a safe use for CEL in heart transplants. To compare CEL against a limited number of control preservation solutions, Cannata *et al*. (19) evaluated 133 patients (CEL 38, HTK 61, and Plegisol 34) and found

Table 2 Selected clinical studies involving cardiac perfusate solutions

Study	Solution	Cases	Patient survival	Graft failure
Remadi (15)	CEL	70	91.4% (30 d)	10%
De Santo (16)	CEL	200	88% (1 y)	–
Wieselthaler (17)	CEL *vs*. HTK	48 (CEL 24, HTK 24)	No diff (CEL 4.2%, HTK 8.3%; P not listed)	No diff (CEL 4.2%, HTK 8.3%)
Vega (18)	CEL *vs*. several	131 (CEL 64, Cntrl 67)	No diff (30 d) (CEL 94%, Cntrl 88%; P not listed)	No diff (30 d) (CEL 6.3%, Cntrl 13.4%; P not listed)
Cannata (19)	CEL *vs*. HTK *vs*. Pleg	133 (CEL 38, HTK 61, Pleg 34)	No diff (in-hosp) (CEL 89.5%, HTK 83.7%, Pleg 85.3%; P=0.717)	No diff (CEL 10.5%, HTK 14.7%, Pleg 14.7%; P=0.814)
Kofler (20)	UW *vs*. HTK	340 (UW 118, HTK 222)	UW > HTK (UW 80.1%, HTK 66.1%; P<0.001)	–
George (21)	UW *vs*. CEL	174 (UW 42, CEL 132)	No diff (1 y) (UW 79.5%, CEL 80.3%; P=0.92)	UW > CEL (UW 0.0%, CEL 10.6%; P=0.02)
Garlicki (22)	UW *vs*. CEL *vs*. HTK	224 (UW 64, CEL 28, HTK 132)	No diff (90 d) (UW 84%, CEL 86%, HTK 88%; P not listed)	UW 9.4%, CEL 0.0%, HTK 4.5%; P not listed
George (23)	UW *vs*. CEL	4,910 (UW 3,107, CEL 1,803)	UW > CEL (UW 89.6%, CEL 87%, P<0.01)	–

Abbreviations: Cntrl, control; no diff, no statistically significant difference; UW, University of Wisconsin; CEL, Celsior; HTK, histidine-tryptophan-ketoglutarate; Pleg, Plegisol; in hosp, in-hospital.

no statistical difference with respect to in-hospital mortality [CEL 10.5%, HTK 16.3%, and Plegisol (St. Thomas) 14.7%, P=0.717] or graft failure (HTK 14.7%, CEL 10.5%, and Plegisol 14.7%, P=0.814).

UW emerged as a popular alternative for heart transplants as there was a survival benefit associated with its use compared to other solutions such as HTK. Kofler *et al.* (20) saw an improvement in survival after switching from HTK to the use of UW in their heart transplant series (UW 80.1% *vs.* HTK 66.1% survival at 1 year, P<0.001). During the transition to UW, that institution also began using nitric oxide and prostanoids to prevent right heart failure which may have imposed confounding effects. An evaluation of 174 patients (42 UW and 132 CEL) found no difference in 30-day/1 year mortality and primary graft dysfunction (UW 11.9% *vs.* CEL 26.5% P=0.059) with the use of UW (21). However, a higher rate of right heart failure was found in the CEL group (UW 0% *vs.* CEL 10.6% P=0.02) (21). Conflicting results were found in an evaluation of 224 patients (UW 64, HTK 132, and CEL 28) where a trend towards lower mortality at 90 days with the use of HTK was observed (UW 16%, HTK 12%, and CEL 14%) (22). Acute graft failure did not occur in the CEL group and was moderate in the UW and HTK groups (UW 9.4%, HTK 4.5%, CEL 0%; P not listed) (22).

The largest study to date was performed by George *et al.* (23) which addressed the mixed results observed between UW and CEL. It comprised 4,910 patients (UW 3,107 and CEL 1,803) and revealed an improvement in 1 year survival with the use of UW (UW 89.6% *vs.* CEL 87.0% P<0.01) (23). Graft survival was not stated (23). Although the improvement in survival is modest, it may account for the lack of statistically significant differences observed by George *et al.* (21) and Garlicki *et al.* (22) as these studies had relatively lower numbers of patients. Together these results suggest that UW should be the preservation solution of choice in heart transplants.

Lung transplantation

The lung can only tolerate a short period of ischemia, usually less than 6 hours (24). Tierney *et al.* (12) reported their experience with lung transplants over a one year duration using EC and prostaglandin E1 with a one year survival of 79%. Oto *et al.* (25) showed no difference in 30-day mortality in 157 lung transplants with the use of EC, Papworth, or PER. However, a follow up study at the same institution with a greater number of patients showed an

Table 3 Selected clinical studies involving lung perfusate solutions. Euro-Collins *vs.* Perfadex/low potassium dextran solutions

Study	Solution	Cases	Patient survival	PaO2/FiO2	Wean from ventilator
Aziz (8)	EC *vs*. PER	69 (EC 37, PER 32)	No diff (30 d) (EC 89.2%, PER 90.7%; P=0.88)	No diff (EC 244 mmHg, PER 266 mmHg; P=0.9)	No diff (EC 71.2 hr, PER 81.9 hr; P=0.4)
Gámez (31)	EC *vs*. PER	136 (EC 68, PER 68)	No diff (30 d) (EC 78, PER 80; P not listed)	No diff (EC 238 mmHg, PER 257 mmHg; P not listed)	No diff (EC 182 hr, PER 174 hr; P not listed)
Müller (32)	EC *vs*. PER	80 (EC 48, 32 PER)	No diff (30 d) (EC 88%, PER 94%; P not listed)	–	No diff (EC 3 d, PER 4 d; P=0.67)
Rabanal (33)	EC *vs*. PER	46 (EC 21, PER 25)	No diff (30 d) (EC 88%, PER 100%; P not stated)	PER > EC (PER 310 mmHg, EC 170 mmHg; P<0.05)	PER > EC (PER 72 hr, EC 92 hr; P<0.05)
Strüber (34)	EC *vs*. LPD	106 (EC 63, LPD 57)	No diff (EC 86%, LPD 92%; P not listed)	No diff (EC 282 mmHg, LPD 303 mmHg; P not listed)	PER > EC (EC 321 hr, LPD 189 hr; P=0.006)
Fischer (35)	(EC *vs*. PER) + PGE1	94 (EC 46, PER 48)	No diff (EC 89.6%, PER 93.5%; P=0.082)	PER > EC (EC 310 mmHg, LPD 370 mmHg; P=0.017)	–

Abbreviations: no diff, no statistically significant difference; PGE1, prostaglandin E1; EC, Euro-Collins; PER, Perfadex; LPD, low potassium dextran; d, day; hr, hours.

increased correlation with long-term death associated with the use Papworth compared to EC or PER in 310 patients [216 double lung transplantations (DLT) and 94 single lung transplantations (SLT)] (11). The effect on mortality is not apparent until after 3 years, potentially accounting for the lack of difference observed among the three perfusate solutions in the Oto's study (25). In both studies there was a lower incidence of primary graft dysfunction observed with PER (11,25). In a larger study comparing multiple solutions, Ganesh *et al.* (26) found no difference in risk adjusted mortality among 681 patients who received EC (284 patients), blood albumin [139], low potassium dextran (LPD) solution (commercially sold as PER), or core cooling (107 patients).

Intracellular preservation solutions were initially used in lung transplants. Hardesty *et al.* (27) compared the use of EC (30 patients) to UW (70 patients) in 100 transplants [13 heart-lung (HLT), 45 DLT, 42 SLT transplants). Both solutions were found to be comparable (27). Given the potential for pulmonary dysfunction from potassium induced vasoconstriction with intra-cellular solutions, extracellular preservation solutions became a topic of interest (28). Thabut *et al.* (29) evaluated 170 patients (124 SLT and 46 DLT) who received UW, EC, Cambridge, or CEL (n=24, 61, 64, and 21 patients, respectively). There was no difference in 1 month mortality however, there was a lower incidence of post-transplant graft edema with the use of Cambridge solution (an extracellular solution) after adjustment for the duration of graft ischemia (29). One of the largest comparison studies involving the use of UW in lung transplants was performed by Arnaoutakis *et al.* (30) who evaluated 4,455 patients (4,161 LPD *vs.* 294 UW) and found an increased risk of mortality at one year with the use of UW (hazard ratio 1.75, P=0.004) after multivariate analysis.

EC has been directly compared to PER (a LPD) in multiple studies (*Table 3*). Aziz *et al.* (8) compared the use of EC and PER in 69 patients (EC 37 and PER 32). There were 12 SLT (EC 7, PER 5), 51 DLT (EC 27, PER 24), and 6 HLT (3 EC, PER 3) (8). There was no difference in the 30-day mortality (EC 10.8% *vs.* PER 9.3%, P=0.88), PaO2/FiO2 ratio (EC 244 *vs.* PER 266 mmHg, P=0.9), or duration of mechanical ventilation (EC 71.2 *vs.* PER 91.9 hr, P=0.4) (8). Similar results were observed by Gámez *et al.* (31) who compared the use of EC to PER in 136 lung transplants [SLT (EC 32, PER 15) and DLT (EC 36, PER 53)] and found no difference in 30-day mortality, length of time on the mechanical ventilator, and PaO2/FiO2 ratio (P values not listed). However, the EC group had a higher incidence (EC 37% *vs.* PER 16%, P=0.01) of severe graft failure (PaO2/FiO2 <150 mmHg) despite a higher number of double lung transplant recipients in the PER group (31).

These results have been refuted by several other studies that have suggested differences between EC and PER. Müller *et al.* (32) evaluated 80 patients who received either EC or PER [46 SLT (EC 31 and PER 15) and 34 DLT (EC 17 and PER 17)]. There was a trend towards improved 30-day mortality (EC 12% *vs.* PER 6%, P not listed) and 1 year

mortality (EC 62% *vs.* PER 79%, P not listed) associated with the use of PER (32). PER was also associated with a favorable reperfusion injury score and improved alveolar/arterial oxygen ratio while the duration of mechanical ventilation was not statistically significant (P=0.67) (32). Rabanal *et al.* (33) evaluated 46 patients undergoing lung transplantation who received EC or PER (EC 21, PER 25 patients). There was no statistical difference in the 30 day mortality between both groups (EC 12% and 0% PER, P not stated), however, there was a better PaO2/FiO2 ratio (EC 170 *vs.* PER 310, P<0.05) and lower duration of mechanical ventilation (EC 92 EC *vs.* PER 72, P<0.05) associated with the use of PER (33). In similar comparisons, Fischer *et al.* (35) also observed a lower PaO2/FiO2 (EC 310, LPD 370 mmHg; P=0.017) with the use of PER while Strüber *et al.* (34) observed a shorter duration of mechanical ventilation (EC 321 *vs.* LPD 189 hr, P=0.006) that correlated with the use of a LPD solution such as PER. Of note, the duration of mechanical ventilation in the Strüber (34) study was substantially longer than other studies such as Rabanal *et al.* (33).

Together these studies suggest against the use of Papworth and UW as they may impose an increased risk of mortality. In comparing two of the most commonly used extracellular preservation solutions in lung transplantation (EC and PER) there does not appear a survival benefit afforded with the use of either solution. However, the improved PaO2/FiO2 and lower duration of mechanical ventilation observed in some studies favor the use of PER.

Conclusions

Based upon the aforementioned studies, UW is superior for cardiac transplantation with a slight survival advantage compared to CEL while PER is the preferred solution for pulmonary transplantations. The use of PER correlates with an improved PaO2/FiO2 ratio and a shorter duration of mechanical ventilation. While we looked at graft survival and overall patient survival, it should be noted that these outcomes are not solely dependent on the preservation solution used. Several variables such as the quality of the graft, surgical technique, and immunosuppression regimen have important contributions to the overall success. Additionally, the survival time point used in our review may not have encompassed the long-term effects associated with the use of a particular preservation solution. Many of the studies were also limited by small sample sizes and may have been underpowered to detect minute differences. The optimal preservation solution for each respective organ can be supported by available evidence based data and might be a useful adjunct to ameliorate the widespread viability observed by Demmy *et al.* (3) among different centers.

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References

1. Belzer FO, Southard JH. Principles of solid-organ preservation by cold storage. Transplantation 1988;45:673-6.
2. Guibert EE, Petrenko AY, Balaban CL, et al. Organ Preservation: Current Concepts and New Strategies for the Next Decade. Transfus Med Hemother 2011;38:125-42.
3. Demmy TL, Biddle JS, Bennett LE, et al. Organ preservation solutions in heart transplantation--patterns of usage and related survival. Transplantation 1997;63:262-9.
4. Mühlbacher F, Langer F, Mittermayer C. Preservation solutions for transplantation. Transplant Proc 1999;31:2069-70.
5. Feng XN, Xu X, Zheng SS. Current status and perspective of liver preservation solutions. Hepatobiliary Pancreat Dis Int 2006;5:490-4.
6. Chambers DJ, Sakai A, Braimbridge MV, et al. Clinical validation of St. Thomas' Hospital cardioplegic solution No. 2 (Plegisol). Eur J Cardiothorac Surg 1989;3:346-52.
7. Divisi D, Montagna P, Jegaden O, et al. A comparative study of Euro-Collins, low potassium University of Wisconsin and cold modified blood solutions in lung preservation in acute autotransplantations in the pig. Eur J Cardiothorac Surg 2001;19:333-8.
8. Aziz TM, Pillay TM, Corris PA, et al. Perfadex for clinical lung procurement: is it an advance? Ann Thorac Surg 2003;75:990-5.
9. Roskott AM, Nieuwenhuijs VB, Dijkstra G, et al. Small bowel preservation for intestinal transplantation: a review. Transpl Int 2011;24:107-31.
10. 't Hart NA, Leuvenink HGD, Ploeg RJ. New Solutions in Organ Preservation. Transplantation Rev 2002;16:131-41.
11. Marasco SF, Bailey M, McGlade D, et al. Effect of donor preservation solution and survival in lung transplantation. J Heart Lung Transplant 2011;30:414-9.
12. Tierney A, Foster R, Ogella D. A perfusionist's role in lung transplant preservation. Perfusion 2004;19:351-7.
13. Wei J, Chang CY, Chuang YC, et al. Successful heart

transplantation after 13 hours of donor heart ischemia with the use of HTK solution: a case report. Transplant Proc 2005;37:2253-4.
14. Southard JH, Belzer FO. Organ preservation. Annu Rev Med 1995;46:235-47.
15. Remadi JP, Baron O, Roussel JC, et al. Myocardial preservation using Celsior solution in cardiac transplantation: early results and 5-year follow-up of a multicenter prospective study of 70 cardiac transplantations. Ann Thorac Surg 2002;73:1495-9.
16. De Santo LS, Amarelli C, Romano G, et al. High-risk heart grafts: effective preservation with Celsior solution. Heart Vessels 2006;21:89-94.
17. Wieselthaler GM, Chevtchik O, Konetschny R, et al. Improved graft function using a new myocardial preservation solution: Celsior. Preliminary data from a randomized prospective study. Transplant Proc 1999;31:2067-8.
18. Vega JD, Ochsner JL, Jeevanandam V, et al. A multicenter, randomized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts. Ann Thorac Surg 2001;71:1442-7.
19. Cannata A, Botta L, Colombo T, et al. Does the cardioplegic solution have an effect on early outcomes following heart transplantation? Eur J Cardiothorac Surg 2012;41:e48-52; discussion e52-3.
20. Kofler S, Bigdeli AK, Kaczmarek I, et al. Long-term outcomes after 1000 heart transplantations in six different eras of innovation in a single center. Transpl Int 2009;22:1140-50.
21. George TJ, Arnaoutakis GJ, Beaty CA, et al. A novel method of measuring cardiac preservation injury demonstrates University of Wisconsin solution is associated with less ischemic necrosis than Celsior in early cardiac allograft biopsy specimens. J Heart Lung Transplant 2012;31:410-8.
22. Garlicki M, Kołcz J, Rudziński P, et al. Myocardial protection for transplantation. Transplant Proc 1999;31:2079-83.
23. George TJ, Arnaoutakis GJ, Baumgartner WA, et al. Organ storage with University of Wisconsin solution is associated with improved outcomes after orthotopic heart transplantation. J Heart Lung Transplant 2011;30:1033-43.
24. Arcasoy SM, Kotloff RM. Lung transplantation. N Engl J Med 1999;340:1081-91.
25. Oto T, Griffiths AP, Rosenfeldt F, et al. Early outcomes comparing Perfadex, Euro-Collins, and Papworth solutions in lung transplantation. Ann Thorac Surg 2006;82:1842-8.
26. Ganesh JS, Rogers CA, Banner NR, et al. Does the method of lung preservation influence outcome after transplantation? An analysis of 681 consecutive procedures. J Thorac Cardiovasc Surg 2007;134:1313-21.
27. Hardesty RL, Aeba R, Armitage JM, et al. A clinical trial of University of Wisconsin solution for pulmonary preservation. J Thorac Cardiovasc Surg 1993;105:660-6.
28. Okada Y, Kondo T. Preservation solution for lung transplantation. Gen Thorac Cardiovasc Surg 2009;57:635-9.
29. Thabut G, Vinatier I, Brugière O, et al. Influence of preservation solution on early graft failure in clinical lung transplantation. Am J Respir Crit Care Med 2001;164:1204-8.
30. Arnaoutakis GJ, Allen JG, Merlo CA, et al. Low potassium dextran is superior to University of Wisconsin solution in high-risk lung transplant recipients. J Heart Lung Transplant 2010;29:1380-7.
31. Gámez P, Córdoba M, Millán I, et al. Improvements in lung preservation: 3 years' experience with a low-potassium dextran solution. Arch Bronconeumol 2005;41:16-9.
32. Müller C, Fürst H, Reichenspurner H, et al. Lung procurement by low-potassium dextran and the effect on preservation injury. Munich Lung Transplant Group. Transplantation 1999;68:1139-43.
33. Rabanal JM, Ibañez AM, Mons R, et al. Influence of preservation solution on early lung function (Euro-Collins vs Perfadex). Transplant Proc 2003;35:1938-9.
34. Strüber M, Wilhelmi M, Harringer W, et al. Flush perfusion with low potassium dextran solution improves early graft function in clinical lung transplantation. Eur J Cardiothorac Surg 2001;19:190-4.
35. Fischer S, Matte-Martyn A, De Perrot M, et al. Low-potassium dextran preservation solution improves lung function after human lung transplantation. J Thorac Cardiovasc Surg 2001;121:594-6.

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Surgical Technique

Heart-lung transplantation

Charles B. Huddleston, Samuel R. Richey

Department of Cardiothoracic Surgery, Saint Louis University School of Medicine, St. Louis, MO, USA

Correspondence to: Charles B. Huddleston, MD. Glennon Hall, 5th Floor, 1465 South Grand Blvd, St. Louis, MO 63104, USA. Email: chuddle7@slu.edu.

Abstract: Heart-lung transplantation itself is not a particularly difficult operation technically. It is the setting in which this procedure is performed which is difficult. The three issues of importance in a successful outcome are appropriate harvest of the heart-lung bloc from the donor, careful explant of the heart and lungs of the recipient, and finally the implant of the heart-lung bloc into the recipient. None of this requires extraordinary technical skill, but does require careful coordination and planning as well as adhering to some fundamental principles. One of the major pitfalls encountered is bleeding related to the explant procedure. Another is graft failure related to harvest and/or the implant procedure. The third is injury to either the phrenic nerve(s) or the left recurrent laryngeal nerve related to the explant procedure. Heart-lung transplantation is a major investment in resources of all sorts including financial, personnel, as well as the organs themselves. It is absolutely imperative that this procedure be performed only by experienced surgeons in centers with established expertise.

Keywords: Technique; transplantation; heart-lung transplantation

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Introduction

Experimentation in heart-lung transplantation was conducted for more than 25 years prior to the first clinical success (1,2). The initial studies in dogs were marked by failures related to altered respiratory pattern in these animals, most likely a consequence of cardiopulmonary denervation. This was not seen when these experiments were performed in primates (3,4). In the late 1960's and early 1970's three attempts at heart-lung transplantation were made. The longest survival of these three was 23 days. Finally in the early 1980's, the group in Stanford successfully transplanted the heart and lungs into three recipients all of whom had pulmonary vascular disease (5). Two of the three were long term survivors of greater than 5 years. The introduction of cyclosporine as an immunosuppressant was felt to be integral in these successful transplants. These patients actually represent the first long term survivors of any sort of lung transplant as clinical isolated lung transplants did not occur until 4-5 years subsequent to this (6). Initially, the majority of heart-lung transplants were for pulmonary vascular disease and cystic fibrosis, diseases primarily treated with lung transplantation alone currently. Fewer and fewer heart-lung transplants have been performed since 1990 when the largest number were recorded in the registry maintained by the International Society of Heart and Lung Transplantation. Less than 100 are performed throughout the world today (7). The role of heart-lung transplantation continues to evolve. Technical problems account for approximately one-fifth of all deaths early following heart-lung transplantation, hence the importance of having a firm grasp on the surgical technique of both the harvest and organ implant.

Donor evaluation and harvest

The donor organs individually must meet the same criteria for donation as for isolated heart and lung transplantation. The heart function must be nearly normal on modest inotropic support at most. There should be no significant valvar stenosis or insufficiency. The chest radiograph should be free of significant infiltrates and the arterial pO_2 on oxygen challenge should exceed 350 mmHg. The donor must be free of systemic infection and have no evidence of

Figure 1 Preparation of the heart-lung bloc. The organs are taken from the cold storage and brought up onto the operative field. The lungs and heart should remain in a slush solution as much as possible during this preparation. All the excess pericardial tissue is removed followed by the esophagus and aortic tissue taken with the organs at the time of the harvest. The trachea is identified and transected at a point approximately 1-2 cartilaginous rings above the takeoff of the right upper lobe bronchus. There is always an impressive collection of mucoid secretions present. These are cultured and then suctioned completely to remove as much as possible (8).

malignancy. Size matching is often difficult because of the relative malnourished state of recipients with end-stage heart and lung disease. A larger donor may be problematic fitting the organs into the chest of the recipient unless there is significant hyperexpansion of the lungs creating a larger thoracic cavity. Recipients with fibrotic lung diseases typically have contracted chest cavities; one should be very cautious of a larger donor in these instances. The lungs can be trimmed or a lobectomy performed to allow for a better fit in some cases. Smaller donors obviously will fit easily but potentially can suffer hyperexpansion pulmonary edema when the mismatch is significant. In general, one is safe to accept a donor 10% above and below the weight of the recipient with a similar height range. Beyond this very limited range, one can expand the accepted donor size based upon the recipient characteristics.

The final evaluation of the donor is on-site with flexible bronchoscopy to evaluate the airways for evidence of aspiration or pneumonia as well as looking for other anomalies. A median sternotomy is performed. The donor heart is examined by direct inspection with the chest open. The pleural spaces are opened widely to allow direct visual and tactile examination of the lungs. The trachea is dissected circumferentially between the aorta and the superior vena cava. Both the superior vena cava and inferior vena cava are dissected out. At the appropriate time, heparin is given intravenously and prostaglandin E1 is administered into the main pulmonary artery. The inferior vena cava is divided and the left atrial appendage is amputated. This allows complete emptying of the heart. The aorta is cross-clamped and both the heart preservative and lung preservative solutions are delivered via cannulae inserted into the ascending aorta and main pulmonary artery respectively. Topical cold saline and slush are applied to the organs. A nominal ventilator rate should be maintained throughout this period of time to enhance the distribution of the pulmoplegia.

The organs are harvested as a heart-lung bloc. The pericardium is divided down to the diaphragm and posteriorly along the diaphragm. The inferior pulmonary ligaments are divided up to the inferior pulmonary veins on each side. The left lung is flipped medially, effectively out of the pleural space allowing access to the posterior mediastinum. The pleura there are divided with a knife and the mediastinal contents are bluntly mobilized including the esophagus and descending aorta. A similar procedure is performed in the right pleural space. The aorta is divided at the level of the innominate artery; a longer segment of aorta can be taken if necessary for any reconstructive purposes in the recipient. The trachea is mobilized further and stapled to occlude it distally at least one centimeter above the carina. The lungs should be mildly inflated at low pressure at the time of application of the stapler. It is then divided proximally while occluded with a clamp of some sort. The esophagus is divided with a GIA type of stapler proximally and distally. The NG tube should have been removed and the endotracheal tube pulled back enough to be excluded from the stapling devices. The descending thoracic aorta is divided. The heart-lung bloc can now be removed from the chest and placed in cold solution, usually the cardioplegia solution, and then placed in cold storage for transport.

Recipient operation

Preparation of the heart-lung bloc

The heart-lung bloc is taken out of cold storage at the appropriate time and all excess mediastinal tissue is removed (*Figure 1*). This includes the mediastinal portion of the esophagus, in addition to the excess aorta and pericardium (*Figure 2A*). The paratracheal tissue of the donor should be left intact to facilitate post-transplant blood supply to the area

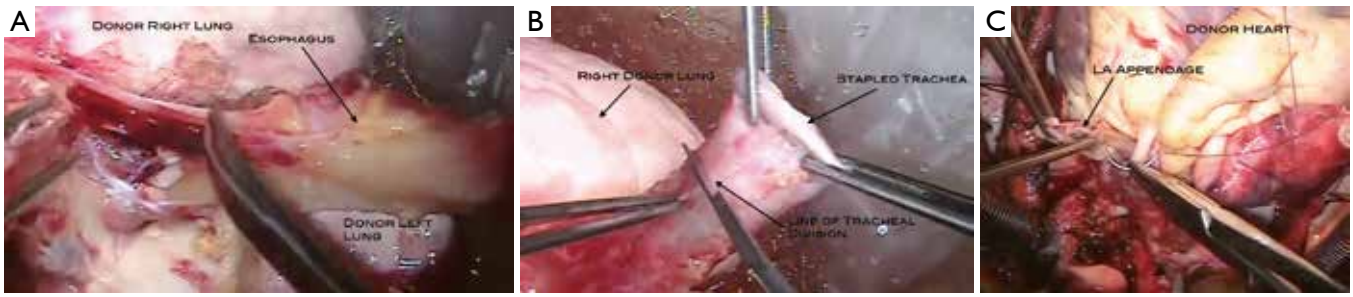

Figure 2 (A) The stapled esophagus is removed by dissecting it away from its mediastinal attachments. The remaining pericardium and aorta have been trimmed away. The trachea is divided above the bifurcation; (B) The trachea is divided above the bifurcation and the staple line is removed; (C) The left atrial appendage which had been amputated is closed with a pursestring to allow the insertion of a catheter for irrigating the left side cardiac structures with cold crystalloid solution.

of the anastomosis. This comes primarily from coronary artery collaterals. The staple line on the trachea is removed leaving one or two cartilaginous rings above the take-off of the right mainstem bronchus for the tracheal anastomosis (*Figure 2B*). A culture of the tracheal secretions is taken and all the retained mucous is suctioned with a separate suction device which will be discarded as soon as the tracheal anastomosis is completed. The amputated left atrial appendage is closed with a pursestring stitch (*Figure 2C*) which is placed on a tourniquet for use during the transplant procedure. This is done while preparing to perform the aortic anastomosis during the transplant procedure. The atrial septum is inspected through the orifice of the inferior vena cava and any defect present should be closed at this point.

Cardiopneumonectomy

In general, a median sternotomy is the optimal approach for heart-lung transplantation. Given the circumstances, one should perform as much of the dissection as possible prior to initiating cardiopulmonary bypass. This is particularly true for patients who have had prior operations. The pleural spaces are opened widely and all adhesions are taken down. Care is taken to preserve the phrenic nerves. The pericardium is opened posterior to the right phrenic nerve as far from the nerve as feasible. The donor lung will be placed posterior to the nerves to get into the respective pleural spaces, so this posterior opening from the pericardium into the pleural space must be along nearly all the length of the phrenic nerves.

The patient is then placed on cardiopulmonary bypass using bi-caval cannulation and cooled to 28 degrees C (*Figure 3*). The cavae are snared and the aorta cross-clamped. The heart is then excised followed by each lung. One can anticipate significant pulmonary venous return via the extensive aortopulmonary collateral network that commonly accompanies patients with the diseases for which heart-lung transplantation is performed. The aorta is divided just above the aortic valve and the main pulmonary artery just above the pulmonic valve. The right atrium is opened with the incision going onto the roof around the right atrial appendage and down toward the coronary sinus. The incision in the roof of the right atrium is taken across into the left atrium and then follows along the atrio-ventricular groove. The atrial septum is divided down toward the coronary sinus. The heart is then removed from the field. Excess right atrium is removed, leaving sufficient cuffs of tissue for the superior and inferior venae cavae anastomoses.

Bilateral pneumonectomies are then performed (*Figure 4*). Each lung is dissected out of the pleural space leaving only the bronchus attached. The pulmonary artery and vein branches do not have to be ligated, but rather can be divided with the electrocautery. The mainstem bronchus is then stapled and the distal bronchus divided. The lungs are then removed from the thoracic cavity. The excess atrial tissue is removed along with any remnants of the proximal branch pulmonary arteries. A sufficient rim of inferior and superior vena cava is necessary for the respective connections with the donor heart (*Figures 5,6*). It is generally advisable to leave a small island of pulmonary artery at the insertion of the ligamentum arteriosum so that risk of injury to the left recurrent laryngeal nerve is lessened. Both mainstem bronchi are then grasped with Allis clamps to assist with the remaining dissection of the distal airway (*Figure 7*). A stay suture is

Figure 3 Recipient cardiectomy. The operation is performed via a midline sternotomy. After dissection of as much of the heart and lungs as possible off bypass, bicaval/aortic cannulation is performed and the patient is placed on cardiopulmonary bypass. The aorta is cross-clamped. The caval tapes are snared. The right atrium is opened in the midportion of the anterior wall. There is a tremendous amount of pulmonary venous return in this case because of an extensive aorto-pulmonary collateral network related to the longstanding cyanosis. The aorta is divided. The atrial incision is taken superiorly around the right atrial appendage and across the atrial septum to the roof of the left atrium. The incision inferiorly is taken toward the coronary sinus. There is no pulmonary artery connection in this patient so that is not divided. The remaining atrial wall holding the heart in is divided and the heart removed from the operative field. This leaves behind the atrial mass (left and right atrial tissue) (9).

Figure 4 Left pneumonectomy. Bilateral pneumonectomies are performed. This video demonstrates highlights from the left pneumonectomy. Adhesions along the pleural surface and mediastinum are taken down with the electrocautery. The inferior pulmonary ligament is divided with the electrocautery and this is further used to go through the pulmonary veins and arteries, rather than taking the time to ligate these vessels; the veins are already open into the pericardium and the only flow into the arteries is via aortopulmonary collateral circulation. The bronchus is dissected free. A stapling device is then applied to the bronchus and it is divided distally. The lung should be able to be removed at this point. A similar procedure is performed for the right lung (10).

Figure 5 Preparation of the IVC and SVC. The remaining atrial tissue is removed. This transplant will be performed using caval anastomoses (rather than a right atrial anastomosis), so as the atrial tissue is removed there should be a sufficient cuff left behind to which the donor SVC and IVC will be sewn. The orifices of the pulmonary veins are easily visible. Liberal use of the electrocautery is evident. Once this tissue is removed, the chest is devoid of the heart and lungs, leaving behind an impressive cavity (11).

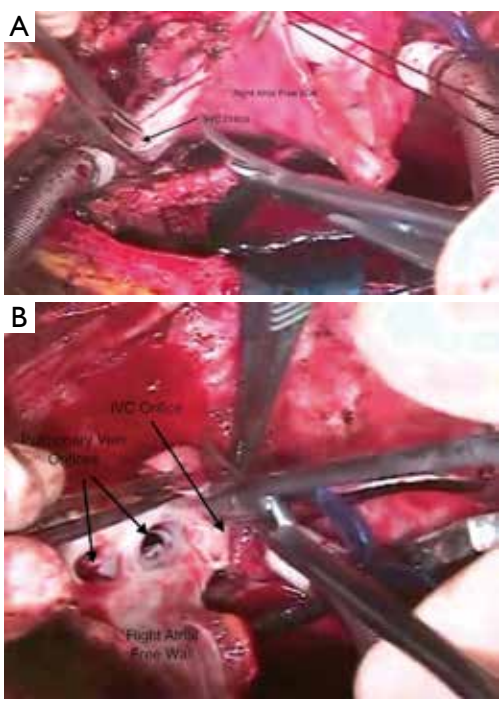

Figure 6 (A) This demonstrates the preparation of the SVC cuff. The excess right atrial tissue is trimmed leaving a sufficient rim for the anastomosis to the donor SVC; (B) Similarly for the IVC a cuff of the right atrium should be left attached to the IVC to allow sufficient tissue and length for the IVC anastomosis to the donor heart. SVC, superior vena cava; IVC, inferior vena cava.

Figure 7 Removal of bronchi and distal trachea. The remaining mainstem bronchi and distal trachea are now excised. The mainstem bronchi are grasped with Allis clamps to assist with the dissection. Placing a stay suture on the more proximal trachea is often helpful for exposure during the tracheal anastomosis. Avoid dissection along the lateral portion of the trachea as much as possible to maintain adequate blood supply to this area. The trachea is divided as distally as possible, remaining cephalad to the mainstem bronchi. Once the anterior wall of the trachea is incised it is obvious from the bleeding that the blood supply is excellent. The remaining portion of the trachea is incised and the distal segment is dissected away from the mediastinum, leaving an open trachea in the mediastinum prepared for the anastomosis (12).

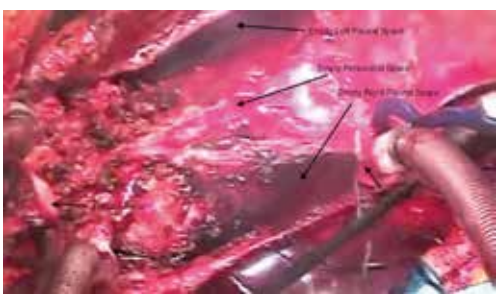

Figure 8 With both lungs and the heart out of the chest the only things remaining are pericardium on both sides to include the phrenic nerves and mediastinal tissue with the lymphatics, esophagus and descending thoracic aorta. Note the large opening posterior to each leaf of pericardium posteriorly to allow the passage of the donor lungs of the heart-lung bloc into the respective thoracic cavities.

placed on the more proximal trachea for traction. The trachea is then divided just above the takeoff of the right mainstem bronchus, which is usually slightly more cephalad than the left. The final step in this portion of the operation is meticulous hemostasis. There are often many mediastinal

Figure 9 Placement of the heart-lung bloc. A pathway has been created posterior to the phrenic nerves on each side. The heart-lung bloc is lowered into the chest passing one lung (the left in this case) into its thoracic space and then the other. Because the lungs remain somewhat inflated, this may require some gentle encouragement to get each lung into its respective position. The heart should be well aligned once this is accomplished (13).

collateral and bronchial vessels which can cause vexing problems with bleeding if not addressed at this point where exposure is optimal. With both lungs and the heart out of the chest, there is an impressive cavity left behind (*Figure 8*).

Transplant procedure

The heart-lung bloc is then lowered into the chest cavity passing the left lung posterior to the phrenic nerve/pericardial pedicle and then the right lung into the left chest posterior to the left phrenic nerve pedicle (*Figure 9*). The order of which lung is passed first is not important. This should place the heart in the midline, lining up the trachea for its anastomotic connection to the recipient trachea. The tracheal anastomosis is done first using a running polypropylene suture (*Figures 10,11*). Some surgeons prefer running the membranous portion and interrupting the cartilaginous portion. When this anastomosis is completed it should be wrapped with whatever viable tissue is in the vicinity, such as pericardium or lymphatic tissue so that the suture line is not up against a vascular structure. This may also provide some additional security against ischemia at the level of the anastomosis. At this point, a catheter is placed into the left atrium via the appendage using the pursestring stitch placed around the amputated left atrial appendage during the preparation of the heart-lung bloc (*Figure 12*). This catheter can be a small vent. It is used to infuse cold crystalloid solution. This keeps the heart cool, but also serves as a way

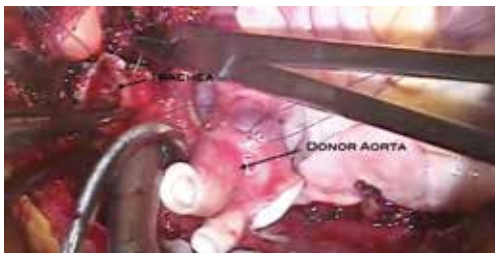

Figure 10 The tracheal anastomosis is the first connection for the heart-lung bloc. This can be done with either a running simple suture technique or using the running technique for the membranous portion and interrupted stitches for the cartilaginous portion of the trachea.

Figure 11 Tracheal anastomosis. This is usually done with a continuous suture of 4-0 polypropylene suture. Other monofilament absorbable suture is certainly reasonable to use as well. Once this is completed, the suture line should be covered with the paratracheal and lymphatic tissue nearby (14).

to evacuate air from the left sided cardiac structures because there is no pulmonary venous return at all during the organ implant of a heart-lung transplant. Next the aortic anastomosis is performed (*Figures 13*,*14*). As this is being completed the cold saline infusing into the left atrium will be coming out the aorta. The cross clamp is then removed and the saline infusion is stopped. The catheter inserted via the left atrial appendage can now be converted to a vent. The inferior vena cava anastomosis is performed next (*Figures 15*,*16*). Alternatively, this could be done with the aortic cross clamp still on; this avoids the nuisance of the coronary sinus blood flooding the operative field. However, it does extend the ischemic time somewhat. The superior vena cava anastomosis is then performed (*Figure 17*). Care must be taken to avoid pursestringing this anastomosis.

Figure 12 Placement of the LA catheter. Prior to performing the aortic anastomosis, a catheter is placed via the left atrial appendage into the body of the left atrium. A standard LV vent is appropriate with an attachment that allows for the instillation of cold crystalloid solution during the aortic anastomosis. This is placed at the site of the LS appendage amputation of the appendage performed at the time of the organ harvest. The infusion of cold crystalloid solution via this catheter keeps the heart cold, but also provides a means of air evacuation. There is no pulmonary venous return to the left atrium until there is antegrade flow through the lungs because the bronchial circulation has been divided. The fluid is run through this catheter at a rate that results in a low flow of fluid from the aorta (15).

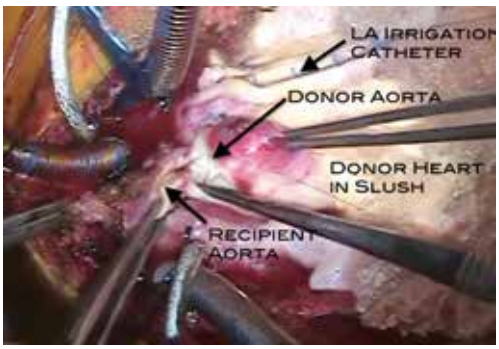

Figure 13 The aortic anastomosis is performed here using a simple running suture technique.

With the completion of all the connections for the new heart-lung bloc, time is taken while on cardiopulmonary bypass to ensure hemostasis. This cannot be emphasized enough. The tissues incised in the process of the recipient cardiectomy and pneumonectomies are all vascular, especially in the setting of cyanotic congenital heart disease or when there have been previous chest

Figure 14 Aortic anastomosis. This is a simple end-to-end connection. As this is being completed the cold crystalloid solution infusing via the LA catheter can be seen coming out of the open portion of the aortic anastomosis. This aids in the de-airing process. Once this is done the aortic cross-clamp can be removed to re-perfuse the heart (16).

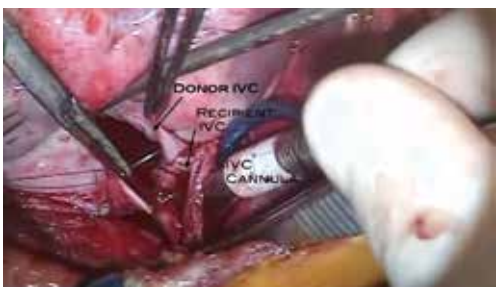

Figure 15 The IVC anastomosis is performed in an end-to-end fashion. IVC, inferior vena cava.

Figure 16 IVC anastomosis. This is generally done with the cross-clamp off the aorta and the heart re-perfused. However, the coronary sinus return to the right atrium often obscures the anastomotic site. This connection is also a simple end-to-end anastomosis (17).

Figure 17 SVC anastomosis. Again, this is a simple end-to-end anastomosis. Care should be taken to avoid pursestringing this anastomosis by interrupting the suture line in three or four locations. If there is significant size discrepancy it is probably better to open the smaller vessel longitudinally and sew on a patch to enlarge this (18).

Figure 18 Functioning transplanted heart and lungs. This merely shows the heart and lungs once off cardiopulmonary bypass. The heart is contracting vigorously and the lungs appear appropriately pink (19).

operations. Bronchial arteries as well as arterial supply to lymphatic tissue are all large and may be difficult to control with the electrocautery alone. This is all performed while on cardiopulmonary bypass to allow manipulation of the heart and lungs to visualize those areas that would otherwise be difficult to see. Ventilation is then initiated and the patient is weaned from cardiopulmonary bypass (*Figure 18*).

Special considerations

Patients with congenital heart disease often present

anatomic challenges when isolated heart transplantation is to be performed. Many of these challenges are eliminated by virtue of the complete evacuation of all mediastinal and chest contents to implant the heart-lung bloc. However, there are some situations that are worthy of mention.

Systemic venous anomalies that might be encountered include bilateral superior venae cavae, interrupted inferior vena cava with azygous continuation to the superior vena cava or hemiazygous continuation to the left superior vena cava, isolated hepatic veins entering directly into the right atrium. In general, all of these entities are best handled by maintaining the route of venous return to the right atrium and performing an atrial anastomosis rather than caval anastomoses. The left superior vena cava returns blood to the right atrium via the coronary sinus. When the recipient cardiectomy is performed the coronary sinus is left intact by trimming off the heart above the coronary sinus at the level of the atrioventricular grove. Azygous continuation of an interrupted inferior vena cava results in a very large superior vena cava that will likely have a significant size mismatch with the donor superior vena cava. Depending upon the size discrepancy, the more practical approach to this may be an atrial anastomosis rather than caval anastomoses.

Situs inversus is another entitiy producing challenges in technical management. Since there is no left atrial anastomosis in heart-lung transplantation, the entire atrial mass can be devoted to the right atrial anastomosis. When the recipient cardiectomy is performed, the atrial septum is removed. A portion of the wall of the anatomic right atrium on the patient's left side is closed, effectively moving the atrial anastomosis to the right, using the recipient anatomic left atrium. The right lung of the donor heart-lung bloc must pass under this atrial mass from left to right to obtain optimal positioning.

Summary

Heart-lung transplant is a procedure performed infrequently even in centers with large heart and lung transplant programs. Those patients often have complex problems that make isolated heart or lung transplant not possible. It is critical that recipients be carefully chosen and that all aspects of the transplant procedure be carefully planned in advance, especially for recipients with congenital cardiac anomalies and have had prior palliative operations. These challenging patients require experienced congenital heart surgeons with expertise in heart-lung transplantation to ensure optimal utilization of these precious organs.

Acknowledgements

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References

1. Webb WR, Howard HS. Cardio-pulmonary transplantation. Surg Forum 1957;8:313-7.
2. Lower RR, Stofer RC, Hurley EJ, et al. Complete homograft replacement of the heart and both lungs. Surgery 1961;50:842-5.
3. Nakae S, Webb WR, Theodorides T, et al. Respiratory function following cardiopulmonary denervation in dog, cat, and monkey. Surg Gynecol Obstet 1967;125:1285-92.
4. Reitz BA, Burton NA, Jamieson SW, et al. Heart and lung transplantation: autotransplantation and allotransplantation in primates with extended survival. J Thorac Cardiovasc Surg 1980;80:360-72.
5. Reitz BA, Wallwork JL, Hunt SA, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med 1982;306:557-64.
6. Patterson GA, Cooper JD, Dark JH, et al. Experimental and clinical double lung transplantation. J Thorac Cardiovasc Surg 1988;95:70-4.
7. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
8. Huddleston CB, Richey SR. Preparation of the heart-lung bloc. Asvide 2014;1:248. Available online: http://www.asvide.com/articles/260
9. Huddleston CB, Richey SR. Recipient cardiectomy. Asvide 2014;1:249. Available online: http://www.asvide.com/articles/261
10. Huddleston CB, Richey SR. Left pneumonectomy. Asvide 2014;1:250. Available online: http://www.asvide.com/articles/262
11. Huddleston CB, Richey SR. Preparation of the IVC and SVC. Asvide 2014;1:251. Available online: http://www.asvide.com/articles/263
12. Huddleston CB, Richey SR. Removal of bronchi and distal trachea. Asvide 2014;1:252. Available online: http://www.asvide.com/articles/264
13. Huddleston CB, Richey SR. Placement of the heart-lung bloc. Asvide 2014;1:253. Available online: http://www.asvide.com/articles/265
14. Huddleston CB, Richey SR. Tracheal anastomosis. Asvide

2014;1:254. Available online: http://www.asvide.com/articles/266
15. Huddleston CB, Richey SR. Placement of the LA catheter. Asvide 2014;1:255. Available online: http://www.asvide.com/articles/267
16. Huddleston CB, Richey SR. Aortic anastomosis. Asvide 2014;1:256. Available online: http://www.asvide.com/articles/268
17. Huddleston CB, Richey SR. IVC anastomosis. Asvide 2014;1:257. Available online: http://www.asvide.com/articles/269
18. Huddleston CB, Richey SR. SVC anastomosis. Asvide 2014;1:258. Available online: http://www.asvide.com/articles/270
19. Huddleston CB, Richey SR. Functioning transplanted heart and lungs. Asvide 2014;1:259. Available online: http://www.asvide.com/articles/271

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Editorial

Overview of paediatric heart-lung transplantation: a global perspective

Yishay Orr

The Heart Centre for Children, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia

Correspondence to: Yishay Orr, MBBS BSc (med) Hon, FRACS, PhD. The Heart Centre for Children, The Children's Hospital at Westmead, Cnr Hainsworth Street and Hawkesbury Road, Westmead, NSW 2145, Australia. Email: yishay.orr@health.nsw.gov.au.

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In this issue of The *Journal of Thoracic Disease* (*JTD*) Jonathon Spahr and Shawn West from the Children's Hospital of Pittsburgh and the University of Pittsburg School of Medicine have presented a perspective on paediatric heart-lung transplantation based on data from their own institution, the Organ Procurement and Transplant Network and supported with data from the International Society for Heart and Lung Transplantation (ISHLT). They have provided a detailed and succinct overview of progress to the current era including indications, contraindications, outcomes and potential future possibilities largely based on the US experience. This editorial aims to extend the review by elaborating on the global perspective of paediatric heart-lung transplantation, particularly in relation to changes in volume and indications over the past 30 years and the influence of organ allocation policies internationally.

The era of human heart-lung transplantation commenced with the first successful adult heart-lung transplant in March 1981 at Stanford University Medical Center (1). This was soon followed by the first successful paediatric heart-lung transplant at Stanford in a 15-year-old girl in 1986 (2). The introduction of cyclosporine in the early 1980s and favourable airway healing rates resulted in good outcomes and heart-lung transplantation rapidly became a popular option for both adult and paediatric patients with end-stage cardiopulmonary disease. Moreover donor organ access was devoid of the current issues related to volume and organ allocation policies. Heart-lung transplant numbers peaked in 1989 with 223 adult (3) and 61 paediatric transplants (4) performed internationally that year (*Figure 1*). Subsequently several changes resulted in a shift away from heart-lung transplantation. Technical issues with isolated lung transplantation were resolved (5) resulting in improved airway healing rates and better survival, and isolated lung transplantation became a viable treatment option for end-stage pulmonary disease in the late 1980s. It also became apparent that survival following combined heart-lung transplant is essentially identical to that for isolated lung transplant with outcome primarily determined by the lung allograft. Moreover, competition for the scarce resource of donor organs and the need for utilitarian distribution of organs also influenced the shift from heart-lung transplantation to isolated lung transplantation in those with structurally normal hearts with preserved function. Consequently isolated single or bilateral lung transplantation became a preferred option for several end-stage pulmonary diseases for which heart-lung transplantation had previously been employed. In children undergoing isolated lung transplantation survival is significantly better with double compared with single lung transplant (6) and consequently bilateral lung transplantation is preferred. Lung transplantation combined with concurrent intra-cardiac repair of congenital heart disease in paediatric patients with Eisenmenger-related end stage pulmonary hypertension has also become an option as experience with lung transplantation has evolved (7). This obviates the need for combined heart-lung transplant but is of course dependent on clinical judgement of the capacity for recovery of ventricular systolic function following lung transplantation and cardiac repair. Finally, medical therapies for pulmonary hypertension have dramatically improved and diversified over the last 30 years thereby delaying or avoiding the need for lung or heart-lung transplantation. In

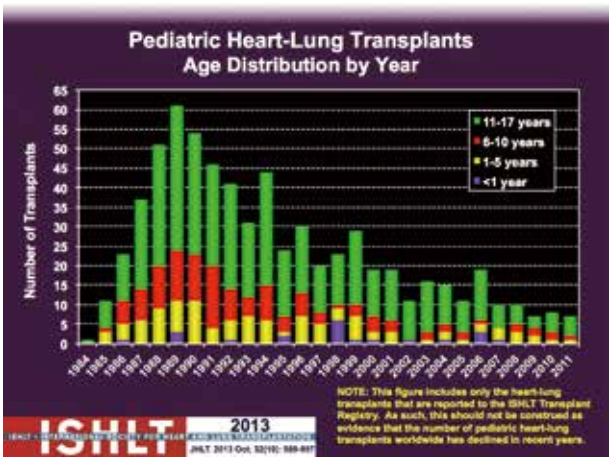

Figure 1 Paediatric heart-lung transplant numbers per year stratified by age distribution (ISHLT Registry Data Report 2013). ISHLT Registry Slides accessed at http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry on 14th June 2014.

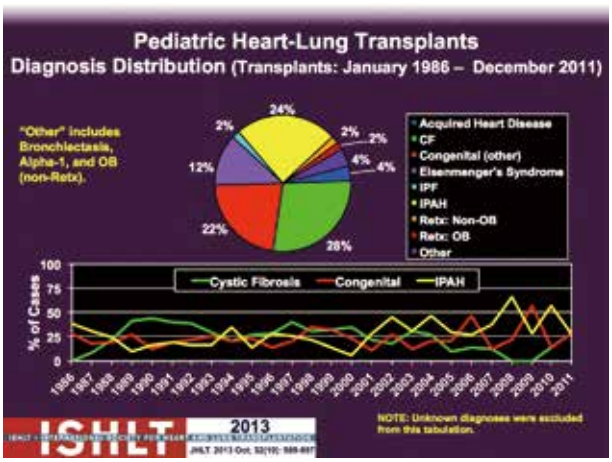

Figure 2 Diagnosis distribution among paediatric heart-lung transplant candidates overall and stratified per year (ISHLT Registry Data Report 2013). ISHLT Registry Slides accessed at http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry on 14th June 2014.

children with end-stage idiopathic pulmonary hypertension and preserved right ventricular function creation of a non-restrictive Potts shunt may also avoid or delay the need for lung or heart-lung transplantation (8).

From a global perspective the most common underlying diagnoses in paediatric heart-lung transplant candidates over the past 30 years have been cystic fibrosis (28%), idiopathic pulmonary arterial hypertension (IPAH, 24%) and congenital heart disease (CHD, 22%) (4) (*Figure 2*). In the early era of heart-lung transplantation the most common diagnosis for paediatric candidates internationally was cystic fibrosis accounting for 40% of heart-lung transplants whereas CHD (15-25%) and IPAH (16%) were less substantial contributors (4) (*Figure 2*). The explanted hearts from those patients with structurally normal hearts and preserved ventricular function could then be used for domino heart transplantation with the advantages of a controlled *ex vivo* organ ischemic time and a donor right ventricle primed to work against elevated pulmonary vascular resistance (9). Airway healing is optimized in patients who undergo heart-lung transplantation as there is preserved bronchial blood supply provided by coronary-bronchial collaterals (1,10) that are not present when the lungs are harvested in isolation. However, increasing technical success with isolated lung transplantation led to this becoming the preferred option for patients with isolated lung disease and domino heart transplants are now rarely performed. Consequently from 1995 onwards the number of paediatric heart-lung transplants performed worldwide decreased substantially from previous highs of 31-61 transplants/year to about 20/yr on average until 2002 when numbers further declined to only 10-15 transplants/year (4) (*Figure 1*). Throughout this time the indications for paediatric heart-lung transplantation have also shifted with cystic fibrosis now only accounting for 0-15% of paediatric heart-lung transplants worldwide whereas IPAH accounts for 27-67% and congenital heart disease for 13-57% (4) (*Figure 2*). However, there are important geographic differences in the relative proportions of underlying diagnoses that likely relate to differences in organ allocation policies and organ availability throughout the world. IPAH and CHD each account for about 40% of paediatric heart-lung transplants in the USA currently whereas in Europe cystic fibrosis, IPAH and CHD are each responsible for about 30% of transplants (*Figure 3*).

Intricacies of organ allocation policies in the USA (11) substantially influence the ability to achieve heart-lung transplantation in both adults and children. Heart-lung candidates must be listed on both heart and lung transplant wait lists as multi-organ candidates. Importantly individuals awaiting heart-lung transplant compete with UNOS status 1A heart-only candidates for the heart component of the organ block. It is rare that a candidate awaiting heart-lung transplant will fulfil criteria for status 1A heart listing thereby significantly limiting access to organs. This can be addressed by applying for an exemption. For paediatric

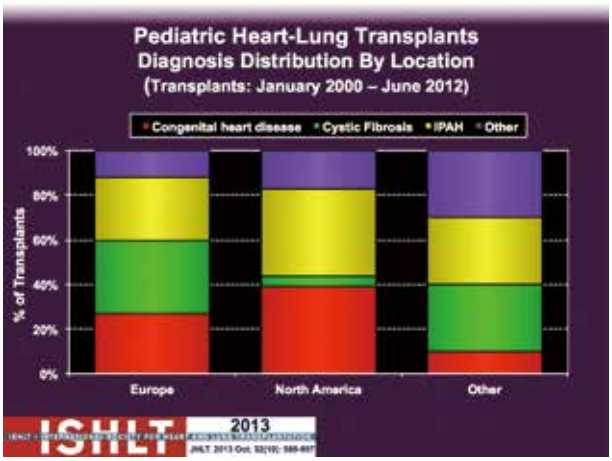

Figure 3 Diagnosis distribution among paediatric heart-lung transplant candidates based on geographic location (ISHLT Registry Data Report 2013). ISHLT Registry Slides accessed at http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry on 14th June 2014.

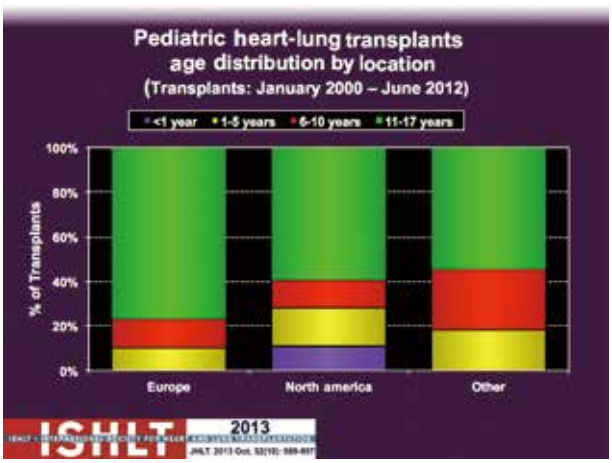

Figure 4 Age distribution among paediatric heart-lung transplant candidates based on geographic location (ISHLT Registry Data Report 2013). ISHLT Registry Slides accessed at http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry on 14th June 2014.

candidates aged 12 years and older a lung allocation score (LAS) is required to define urgency for the lung component of the heart-lung block. Similar to heart urgency these candidates often do not fulfil criteria to achieve a high LAS and therefore may be disadvantaged. In contrast, the Eurotransplant policy (12) prioritizes heart-lung candidates above heart-only candidates with the same level of urgency in most European countries thereby optimizing access for the multi-organ candidates. Importantly, allocation policies in both Europe and the USA prioritize paediatric organs (donor <18 years of age) to paediatric recipients.

Infant heart-lung transplantation is essentially only performed in centres in the USA (*Figure 4*), a scenario that parallels the practice of infant lung transplantation. ISHLT data suggests that outcome following infant heart-lung transplantation is very poor with essentially no survivors beyond one year (13). However, under-reporting and incomplete reporting of outcomes likely influences this data. Moreover, it is not consistent with prior reports of acceptable early and medium term survival following infant heart-lung transplantation (14,15). Median graft survival following infant isolated lung transplantation in the USA is 4 years and is equivalent to other paediatric age groups (16). Median graft survival conditional on one-year survival is excellent at 7.4 years for infant lung transplantation (16). It is likely that survival following infant heart-lung transplant in the current era should be similar to that following infant lung transplant as heart-lung transplant outcome is defined by lung allograft survival. However, no infant heart-lung transplants have been reported to ISHLT since 2007 (4), likely for many of the general reasons mentioned previously, and most were performed in the decade from 1998-2007. The ability to repair or palliate complex CHD involving pulmonary vascular abnormalities has improved substantially over time thereby avoiding the need to perform heart-lung transplantation as primary intervention for CHD in infants. Finally, some patients may be amenable to intra-cardiac repair combined with infant lung transplantation given the difficulty in accessing a donor heart-lung block in the USA.

There are essentially two primary clinical indications for paediatric heart-lung transplantation in individuals with end-stage cardiopulmonary disease being limited life expectancy and poor quality of life. Those individuals with an estimated life expectancy of 1-2 years based on objective data such as FEV_1, $VO_{2(max)}$, 6-minute-walk distance and supra-systemic pulmonary artery pressures should be considered for listing. The subgroup of infants is unique in that many of these candidates are dependent on invasive ventilation, inotropes and other supportive therapies, and therefore have a constant threat to life. Secondly, candidates with a poor quality of life as indicated by markedly limited physical activity, inability to attend school, inability to perform normal activities such as walking and playing with friends, dependency on inhaled oxygen therapy or non-invasive ventilation and frequent hospital admissions

should also be considered for transplantation. Of course the standard requirements for transplant candidacy such as demonstrated compliance, good carer support and the absence of clinical contra-indications also need to be verified. In particular, adequate parental support, engagement and compliance is essential to a successful outcome following paediatric thoracic transplantation and its importance cannot be over-emphasized.

There are few absolute contraindications to heart-lung transplantation outside of the standard issues such as active or recent malignancy, active high-risk infection or multi-system organ failure. However many centres would be reluctant to offer heart-lung transplant to a patient dependent on veno-arterial extra-corporeal membrane oxygenation (VA-ECMO). This is particularly true for infants supported on VA-ECMO who have a very high pre-transplant mortality (14). This philosophy is changing somewhat in paediatric patients (17) as experience with lung and heart-lung transplantation in adults supported with awake, extubated VA-ECMO increases in high volume centres (18,19). It is important to emphasize that the need for VA-ECMO indicates dual organ failure and carries higher risk of complications and mortality than veno-venous ECMO for isolated respiratory failure with preserved cardiac function. Heart-lung transplantation may be utilized in situations where isolated lung transplant is not an option such as congenital pulmonary vein stenosis previously managed by sutureless repair or other techniques that prevent safe and adequate explantation of the native lungs with preservation of the phrenic nerves. Absence of native intra- and extra-pericardial pulmonary arteries is a contra-indication to isolated heart transplantation that has been addressed by using heart-lung transplantation in patients with lesions such as pulmonary atresia, ventricular septal defect and major aorto-pulmonary collaterals (PA/VSD/MAPCAs). Unfortunately, early outcomes in this patient population are poor due to a high risk of intra-operative exsanguination from extensive systemic to pulmonary collateral vessels, particularly in the setting of previous thoracotomies and sternotomies for palliative or corrective procedures. Consequently many experienced centres consider PA/VSD/MAPCAs to be an absolute contraindication to heart-lung transplantation (20).

It is important to clarify that heart-lung transplantation, like many solid organ transplants, is not a cure but is instead a form of palliation. This is particularly important to emphasize for anyone receiving a lung allograft as median survival following paediatric lung or heart-lung transplant still remains poor at approximately 5 years (6). Despite extensive investigation we remain limited in our ability to prevent or treat the inevitable development of bronchiolitis obliterans syndrome and chronic lung allograft dysfunction. Nevertheless combined heart-lung transplant continues to be a valuable therapeutic option for those with a poor quality of life or at high risk of dying as long as the recipient and their family accept its limitations.

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References

1. Jamieson SW. Combined heart and lung transplantation. West J med 1985;143:829-33.
2. Deuse T, Sista R, Weill D, et al. Review of heart-lung transplantation at Stanford. Ann thorac Surg 2010;90:329-37.
3. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:965-78.
4. Benden C, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart-lung transplantation report--2012. J Heart Lung Transplant 2012;31:1087-95.
5. Cooper JD. The evolution of techniques and indications for lung transplantation. Ann Surg 1990;212:249-55.
6. Benden C, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Lung and Heart-Lung Transplantation Report--2013; focus theme: age. J Heart Lung Transplant 2013;32:989-97.
7. Choong CK, Sweet SC, Guthrie TJ, et al. Repair of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: a 13-year experience. J Thorac Cardiovasc Surg 2005;129:661-9.
8. Baruteau AE, Serraf A, Lévy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: long-term results. Ann Thorac Surg 2012;94:817-24.
9. Klepetko W, Wollenek G, Laczkovics A, et al. Domino transplantation of heart-lung and heart: an approach to overcome the scarcity of donor organs. J Heart Lung

Transplant 1991;10:129-31.
10. Singh SP, Nath H, McGiffin D, et al. Coronary tracheal collaterals after heart-lung transplant. Am J Cardiol 2003;92:1490-2.
11. Organ Procurement and Transplantation Network (OPTN) Policies. Policy 6: Allocation of Hearts and Heart-Lungs. 2014.
12. Chapter 6: ET Thoracic Allocation System (EThAS). In: Eurotransplant manual version 3.3. 2014. Available online: https://www.eurotransplant.org/cms/index.php?page=et_manual
13. Aurora P, Edwards LB, Christie JD, et al. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Lung and Heart/Lung Transplantation Report-2009. J Heart Lung Transplant 2009;28:1023-30.
14. Ro PS, Spray TL, Bridges ND. Outcome of infants listed for lung or heart/lung transplantation. J Heart Lung Transplant 1999;18:1232-7.
15. Starnes VA, Oyer PE, Bernstein D, et al. Heart, heart-lung, and lung transplantation in the first year of life. Ann Thorac Surg 1992;53:306-10.
16. Khan MS, Heinle JS, Samayoa AX, et al. Is lung transplantation survival better in infants? Analysis of over 80 infants. J Heart Lung Transplant 2013;32:44-9.
17. Wong J, Buchholz H, Conradi A, et al. Successful Modified Semi-Ambulatory Veno-Arterial Extracorporeal Membrane Oxygenation (VA ECMO) Bridge To Heart-Lung Transplantation (HLTx) In A Four Year Old Child With Idiopathic Pulmonary Hypertension (IPAH). Am J Resp Crit Care 2012;185:A5824.
18. Olsson KM, Simon A, Strueber M, et al. Extracorporeal membrane oxygenation in nonintubated patients as bridge to lung transplantation. Am J Transplant 2010;10:2173-8.
19. Abrams DC, Brodie D, Rosenzweig EB, et al. Upper-body extracorporeal membrane oxygenation as a strategy in decompensated pulmonary arterial hypertension. Pulm Circ 2013;3:432-5.
20. Goerler H, Simon A, Gohrbandt B, et al. Heart-lung and lung transplantation in grown-up congenital heart disease: long-term single centre experience. Eur J Cardiothorac Surg 2007;32:926-31.

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