Curr Cardiol Rep (2016) 18: 36
DOI 10.1007/s11886-016-0713-1

State of the Art of Combined Heart-Lung Transplantation for Advanced Cardiac and Pulmonary Dysfunction

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Published online: 27 February 2016
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Abstract Over the last several decades, significant advances and improvements in care of transplant patients have resulted in markedly improved outcomes. A number of options are available for patients with advanced cardiopulmonary dysfunction requiring transplantation. There is a debate about when isolated heart or isolated lung transplantation is no longer possible or advisable and combined heart-lung transplantation is justified. Organ availability and allocation severely limit the latter option to very few well-selected patients. We review practice patterns, trends, and outcomes after triple-organ heart-lung transplant (HLTx) worldwide, as well as our own experience with heart-lung transplant in the modern era.

Keywords Heart-lung transplant · Eisenmenger · Pulmonary hypertension · ECMO · Heart failure · Cardiac and pulmonary dysfunction · Only option

Introduction

Over the last few decades, thoracic organ transplantation has been on the rise for treating patients with intractable cardiac and/or pulmonary disease [1••, 2–14]. Although isolated heart or lung transplantation is possible for most patients with advanced cardiopulmonary disease, triple-organ heart-lung transplant (HLTx) remains the only or best option for a few patients [1••, 2–4].

The use of HLTx peaked in 1989, when 284 adult HLTx were performed. Use of HLTx subsequently declined steadily but has plateaued to an annual rate of 62–94 for the most recent decade. In 2012, a total of 75 adult HLTx were performed, suggesting that for a distinct subset of patients, there is no other therapeutic choice than HLTx. According to the official report from the International Society for Heart and Lung Transplantation (ISHLT) 2014, the most common indication for HLTx is congenital heart disease with progressive pulmonary hypertension resulting in cardiopulmonary dysfunction. In 2014 alone, over 3700 single-lung or bilateral lung transplants and over 4000 isolated heart transplants were performed worldwide [1••].

There is a continued debate about when HLTx offers an important benefit over isolated lung transplantation [15, 16••, 17–20, 21••, 22, 23]. Our objectives are to review the current trends and outcomes after HLTx, to define its role in current practice, and to guide appropriate and optimal patient selection.

World Experience with Heart-Lung Transplantation

Indications and Patient Characteristics

A total of 3767 adult heart-lung transplants have been performed worldwide from January 1982 to June 2013, according to the latest (2014) report from the ISHLT [1••]. Approximately two thirds of the patients were treated for congenital heart disease (35.5 %) and idiopathic pulmonary artery hypertension (IPAH; 27.4 %). This proportion has remained

This article is part of the Topical Collection on *Congenital Heart Disease*

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constant throughout the period, and these pathologies are the dominant indications for HLTx at both US and European centers. Comparing the most recent decade (2002–2013) to the previous decade (1982–1991), the proportion of patients undergoing HLTx for acquired cardiovascular disease has progressively increased (from 2.6 to 10.6 %), whereas the number of patients with cystic fibrosis undergoing HLTx has decreased (6.8 vs. 17.2 %), more so in USA than in Europe. Today, the vast majority of patients with cystic fibrosis undergo bilateral lung transplants [1••]. There are several reasons for this development; organ allocation rules severely limit the availability of heart-lung blocks, the logistics around domino transplantation of a good recipient heart are too complicated, and finally, cystic fibrosis patients do equally well with double-lung transplant only. The reason is not necessarily transplant at an early disease stage; the development has rather gone in the opposite direction.

Trends in Outcomes

Early Mortality and Long-Term Survival

Since the early 1980s, when the HLTx was first performed, the outcomes have improved with each subsequent era [1••, 2–15, 16••, 17–20, 21••, 22–25, 26••, 27, 28]. Dawkins et al. published their initial 3.5 years of experience with 22 HLTx patients at Stanford in 1985 [1••, 5]. Twelve of the patients underwent HLTx for Eisenmenger syndrome with congenital heart disease and the remaining 10 had IPAH. They reported a 26 % in-hospital or 30-day mortality and an actuarial survival of 71 % at 1 year and 57 % at 2 years. Data on survival reported from the ISHLT Registry for the same era (1982–1991) consisted of 1216 patients and the outcomes were similar. The operative mortality was 25.4 % and the survival at 1, 2, 5, and 10 years were 56, 49, 37.7, and 26 %, respectively [1••, 2–4, 15]. In contrast, the 2014 report demonstrates major improvements in survival in the most recent decade (2002–2012), with an operative mortality of 16.8 % and survival at 1, 2, 5, and 10 years of 69, 62, 51, and 43 %, respectively [1••]. Even though late survival has improved, the most significant improvements are noted during the early post-transplant periods. In patients who survive the first year post-transplant, the conditional median survival is 10.3 years. These improvements are attributable to better patient selection, refinement of surgical techniques, immunosuppressive therapy preventing graft rejection, and improved understanding of risk factors for morbidity and mortality [15, 16••, 17–20, 21••, 22, 29–33].

Causes and Predictors of Mortality

Longer-term outcomes after HLTx are in essence identical to outcomes after lung transplantation, though significantly worse than after heart transplantation, and most complications after HLTx are lung-related. Therefore, post-operative management is more similar to lung transplantation than heart transplantation; the lungs seem to protect the heart by absorbing immune-mediated damage.

Although the overall mortality rate has declined over time, the causes of death have remained similar across each era [1••, 2–4]. The most common causes of death in the initial 30-day period are due to post-transplant graft failure, technical complications, and infection, whereas bronchiolitis obliterans syndrome (BOS) and chronic lung allograft dysfunction (CLAD) remain the major causes of mortality after 1 year. Patients requiring mechanical ventilation or circulatory support prior to HLTx do worse than those who do not. Jayarajan and colleagues analyzed the United Network for Organ Sharing (UNOS) database of HLTx from 1995 to 2011 and reported that HLTx patients requiring pre-transplant ventilation or extracorporeal membrane oxygenation (ECMO) support had worse survival compared to matched controls at 1 month (20 vs. 83.5 %, if on ECMO) and at 5 years (20 vs. 45.4 %, $p < 0.0001$) post-transplant, clearly substantiating the difference in outcomes based on pre-operative disease severity [16••].

Since the total number of HLTx performed per year is low, only a few studies have performed risk factor analysis of mortality and the findings are limited. Recent ISHLT data analysis showed that older age of the donor and indications other than IPAH are predictors of mortality. Center volume was not a statistically significant risk factor, but no center does a large number of HLTx, and most centers, like ours, bundle HLTx with lung transplant. A robust data analysis of patients undergoing single-lung or bilateral lung transplant using the ISHLT Registry has shown that the severity of illness (pre-transplant intensive care, mechanical ventilation, or dialysis), donor diabetes, CMV mismatch, prior recipient transfusion history, center volume, donor-recipient height difference, higher bilirubin, low cardiac output, and higher creatinine are strongly associated with mortality [1••, 2–4]. These findings are most likely also applicable for predicting risk in HLTx patients.

Late Complications, Graft Rejection, and Retransplantation After HLTx

The most common causes of morbidity after HLTx are associated with the long-term effects of immunosuppressive therapy. Yusen and colleagues analyzed HLTx patients in ISHLT Registry (1994–2013) and showed that at 5 years, post-transplant hypertension (88.1 %) and hyperlipidemia (70 %) were extremely common. More importantly, renal dysfunction occurred in 45.5 %, including 2.1 % who required dialysis and 1.1 % who required kidney transplant. Consistent with the fact that most early complications are pulmonary, BOS in the lungs was much more common than coronary vasculopathy (28.7 vs. 8.2 %). There were 90 retransplantations after HLTx

performed from 1982 to 2012 (ISHLT Registry) with survival at 3 months, 1, 3, and 5 years of 52, 43, 36, and 27 %, respectively, suggesting that retransplantation after HLTx does not seem to be a good therapeutic option [1••, 2–4].

Cleveland Clinic Experience with Heart-Lung Transplant

From 1992 to 2014, 34 patients underwent HLTx at Cleveland Clinic for congenital heart disease with Eisenmenger's syndrome ($n=8$), congenital heart disease with elevated pulmonary vascular resistance ($n=8$), idiopathic pulmonary arterial hypertension ($n=9$), sarcoidosis ($n=2$), cystic fibrosis with tetralogy of Fallot ($n=1$), idiopathic pulmonary fibrosis ($n=1$), radiation heart-lung disease ($n=1$), COPD-alpha 1 deficiency ($n=1$), chronic pulmonary embolism ($n=1$), and failure of previous lung transplant due to BOS and ischemic cardiomyopathy with right heart failure ($n=2$). Mean age of the patients was 31 ± 16 years and median time from referral to transplant was 194 days (statuses 1A:12, 1B:12, and II:10). Thirteen (38 %) patients required ICU admission prior to transplant, 5 (15 %) were on ECMO, and 2 (6 %) had a tracheostomy at the time of HLTx. Median follow-up was 4.1 years (range 1–22 years). Donor selection and matching were performed using the standard heart and lung selection criteria. When it comes to donor organ function, our priority is good heart function and match over the lungs. The surgery may require some preparedness to deal with surprises and unusual anatomical and technical challenges (Fig. 1). Expeditious surgery and good hemostasis are critical for success. Additional details regarding patient characteristics are listed in Table 1.

Results

Mean cardiopulmonary bypass time was 169 ± 62 min. Five (15 %) patients required immediate post-operative ECMO—four of these five patients (80 %) requiring ECMO after transplant died. Overall hospital and 30-day mortality was 15 % (5/34). Causes of death were bleeding and coagulopathy ($n=2$, 6 %), intra-vascular thrombosis ($n=1$, 3 %), pulmonary artery thrombosis ($n=1$, 3 %), and sepsis leading to multi-organ failure ($n=1$, 3 %). Other early post-operative complications included sepsis ($n=2$, 6 %), pneumonia ($n=3$, 9 %), myocardial infarction ($n=2$, 6 %), renal dialysis ($n=9$, 26 %), and reoperation for bleeding ($n=10$, 30 %) but no stroke or pulmonary embolism. There were eight late deaths. Causes of late death included acute rejection ($n=2$), bronchiolitis obliterans ($n=3$), myopathy, renal cancer, and disseminated aspergillosis (one each). Estimated survival at 1, 3, 5, 10, and 15 years were 82, 69, 62, 54, and 54 %, respectively (Fig. 2).

Our outcomes are similar to previous reports on HLTx. It is important to note that patients requiring ICU care or ECMO support, both pre- and post-HLTx, did poorly after HLTx. Patients who were stable when transplanted had very good outcomes, which highlights the importance of proper patient selection and allowing patients to be transplanted before they become too sick, deconditioned, and in need of cardiopulmonary support.

Heart-Lung vs. Bilateral Lung or Single-Lung Transplant

Most patients presenting for consideration of HLTx have advanced cardiac dysfunction in the setting of pulmonary hypertension. The two most common clinical scenarios are congenital heart disease with advanced pulmonary hypertension and shunt reversal (Eisenmenger syndrome) and primary pulmonary hypertension presenting with advanced right heart failure [15, 16••, 17–20, 21••, 22–25, 26••, 27–37]. Currently, there are limited guidelines and minimal data available to guide decision-making for the procedure of choice in these patients. Single-organ transplant, whenever possible, offers shorter wait times and better chance of being transplanted. Several institutions have reported their experience and outcomes, providing important insights regarding patient selection.

General Practice Patterns—Indications for HLTx

HLTx has been the preferred procedure in patients with congenital heart disease and Eisenmenger's syndrome, but procedure selection and preferences are variable, particularly in patients with advanced pulmonary disease. Pielsticker and colleagues reviewed the practice patterns for treatment of pulmonary hypertension with lung transplant vs. HLTx in North America, Europe, and Israel by surveying 35 centers, 29 with a transplant program. Sixty-nine percent of the centers were in the USA. Altogether, 784 lung and 71 HLTx were performed annually. Overall, no institution preferred single-lung over bilateral lung transplant or HLTx. The preference of double lung or HLTx varied according to geographic region. One-hundred-percent preference was given to double-lung transplant over HLTx in USA and Canada, whereas 71 % preferred HLTx over bilateral lung transplant in Europe and Israel. This difference in practice was largely due to allocation in hearts, making it very difficult to get a heart-lung block in USA and Canada [18].

Heart-Lung vs. Bilateral Lung Transplant with Congenital Cardiac Repair

Selected patients who are amendable to congenital repair may be candidates for concurrent isolated lung transplant as an alternative to HLTx. Choong and colleagues reported their experience with congenital heart disease in pediatric patients undergoing HLTx ($n=16$) vs. bilateral lung transplant with concurrent or prior congenital repair ($n=35$). The anomalies in the congenital repair group most commonly included

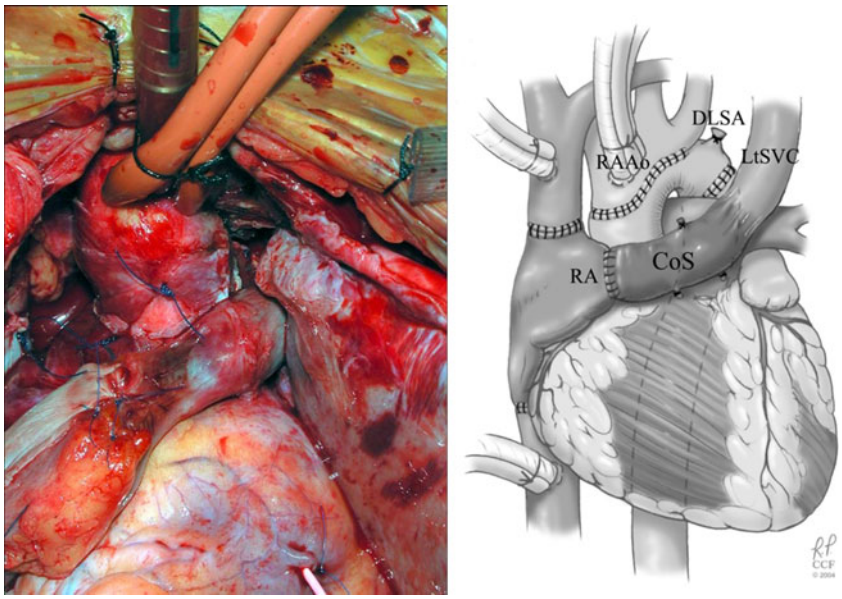

Fig. 1 Heart-lung transplant in a patient with complex congenital disease and Eisenmenger syndrome

ventricular septal defect (VSD), pulmonary venous obstruction, and pulmonary atresia. At 1, 3, and 5 years, the long-term survival (HLTX 66.5, 66.5, and 60 % and bilateral lung transplant 62.9, 51.4, and 51.4 %; $p=0.852$) and freedom from BOS (HLTX 77.8, 51.9, and 38.9 % and bilateral lung transplant 72.9, 54.7, and 54.7 %; $p=0.442$) were similar between the two groups, respectively. It must be noted, however, that patients in this study were highly selected, and in 20 % of the patients, the congenital repair was performed prior to lung transplant. Also, patients with more complex multiple congenital anomalies preferably underwent HLTx. In their experience, lung transplant with concomitant heart defect repair was only considered when the repair was deemed possible without adding ischemic time in excess of 60 min [38•].

Several other studies have reported better outcomes after HLTx vs. bilateral lung or single-lung transplant with/without congenital repair in patients with congenital heart disease and Eisenmenger's syndrome. Waddell and colleagues analyzed the United Network for Organ Sharing and International Society for Heart and Lung Transplantation Registry and compared long-term outcomes among 430 HLTx patients vs. 106 bilateral lung transplant and 69 single-lung transplant for congenital heart disease with Eisenmenger's syndrome. Multivariable analysis showed that there was a significant benefit of HLTx over lung transplant in patients with VSD (risk ratio 0.517, $p=0.0001$, HLTx 1.817, $p=0.035$, lung transplant), and 1-year survival was also significantly better in the HLTx group when it was performed in patients with VSD (71.4 %) and multiple congenital anomalies (77.6 %, $p=0.011$) [26••]. Studies comparing outcomes of HLTx for Eisenmenger's syndrome vs. non-Eisenmenger's syndrome indications have shown that HLTx is safe and effective without significant differences in outcomes [30–33, 35–37].

Heart-Lung vs. Lung Transplant for Pulmonary Hypertension with Right Heart Failure

Bando and colleagues reported their outcomes after single lung, bilateral lung, and HLTx for primary pulmonary hypertension ($n=27$) and for Eisenmenger syndrome ($n=30$). Preference was given to HLTx in patients with left ventricular ejection fraction less than 35 %, significant coronary artery disease, or complex congenital anomaly with Eisenmenger's syndrome. They reported no difference in mortality at 1–3 months among all three groups, but the single-lung transplant patients had worse survival at 1 year (58 %) and significantly higher incidence of graft failure (single lung 30 %, double lung 65 %, and HLTx 80 %; $p<0.05$). In addition, the single-lung group also had worse functional recovery and higher post-operative pulmonary artery pressures, lower cardiac index, longer periods of assisted ventilation, and longer ICU stays. In contrast, there were no significant differences in outcomes between HLTx and bilateral lung transplant; other than ischemic times were shorter and cardiac function was better in the HLTx group. In another study by Fadel and colleagues, outcomes of 152 HLTx patients were compared to outcomes of 67 patients who underwent bilateral lung transplant. Even though the HLTx patients had more severe disease (more severe right ventricular dysfunction, worse liver or kidney function, and requiring more inotropic support; $p<0.05$ each), they reported no difference in survival at 1, 5, 10, and 15 years, respectively, between the two groups (HLTx 70, 50, 39, and 26 % vs. bilateral lung transplant 79, 52, 43, and 30 %; $p=0.46$). Ten-year freedom from BOS-related death was better in the HLTx group (79 %) vs. bilateral lung transplant (74 %, $p=0.035$). In a most recent multi-institutional analysis conducted by Hill and colleagues, long-term survival was compared between 261 HLTx patients and

Table 1 Patient characteristics and outcomes of heart-lung transplants at Cleveland Clinic

	$N = 34$
Patient characteristics	
Age	36 ± 15 years
Female	14 (41)
BMI	23 ± 4
Congestive heart failure	27 (79)
Transfusion history	7 (21)
Tracheostomy	5 (15)
Prior cardiac surgery	9 (26)
Indications for heart-lung transplant	
Eisenmenger's syndrome	8 (24)
Congenital heart disease with pulmonary vascular resistance	8 (24)
Idiopathic pulmonary arterial hypertension	9 (26)
Sarcoidosis	2 (5)
Cystic fibrosis with tetralogy of Fallot	1 (5)
Idiopathic pulmonary fibrosis	1 (3)
Radiation heart-lung disease	1 (3)
COPD with alpha anti-trypsin deficiency	1 (3)
Chronic pulmonary embolism	1 (3)
Failure of previous lung transplant	2 (5)
Timing (median, days)	
Referral to inclusion in list	70 (0–1047)
Inclusion in list to treatment	115 (2–1134)
Referral to treatment	194 (1–1275)
Urgency	
Status 1A	12 (35)
Status 1B	12 (35)
Status 2	10 (29)
Outcomes	
Hospital and 30-day mortality	5 (15)
CPB time (min)	169 ± 62
Median operative length of stay (day)	18 (11–100)
Median ICU length of stay	6 (1–46)
Post-operative complications	
Sepsis	2 (5.9)
Coma	1 (2.9)
Myocardial infarction	2 (5.9)
Renal dialysis	9(26)
Pneumonia	3(8.8)

667 bilateral lung transplant patients using the Scientific Registry of Transplant Recipients database. Their findings confirmed previous reports showing that there was no difference in overall survival between the two groups. However, in the subset of patients hospitalized in the ICU prior to transplantation, there was a statistically significant survival benefit of HLTx over bilateral lung transplant (40 vs. 20 % at 8 years, $p = 0.043$). As such, it appears that patients with severe right heart failure overall do better with HLTx compared to lung transplantation alone.

Timing of Heart-Lung Transplant for Congenital Heart Disease

It is estimated that 75–85 % of the patients with congenital anomalies are able to survive to adulthood and about 10–20 % will end up requiring transplantation at some point in their life [35–37]. The optimal timing and decision making for transplantation is dependent upon a number of important factors, such as underlying pathology, disease severity, and organ availability. The optimal timing of HLTx, however, remains

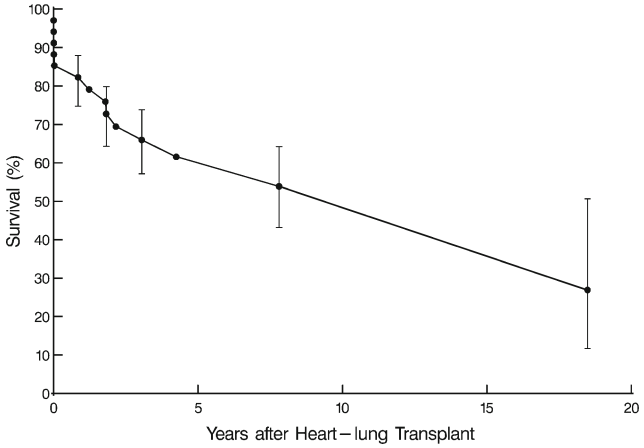

Fig. 2 Long-term survival after heart-lung transplant at the Cleveland Clinic

a significant controversy. Patients who survive to adult life are often well-adapted to their limited working capacity and present late in the course of the disease for consideration of transplantation. The current guidelines of risk stratification scores for heart failure do not readily apply to these patients.

The long-term survival in patients with Eisenmenger syndrome is unpredictable and patient specific. The current general guidelines recommend transplantation based upon a predicted life expectancy of 2 years or less despite optimal medical therapy and in the absence of contraindications. Hosseinpour et al. described the "grown-up" congenital heart disease patients by categorizing them into three groups based on pathophysiology at presentation: (1) patients with uncorrected defects, (2) previous successful congenital repair, and (3) a failing prior palliative repair [36]. When reviewing treatment options in these groups, an assessment of progressive deterioration of ventricular dysfunction and pulmonary hypertension should prompt referral for HLTx, and a decision should be based on evaluation of cardiac anatomy, hemodynamics, and the overall health of the patient. As a general guideline in these patients, it is recommended that isolated heart transplant be considered if pulmonary vascular resistance is 5 Wood units or less and/or the transpulmonary pressure gradient is less than 12 mmHg [35–37]. It should also be noted that many congenital heart disease patients present with their own unique complications and pathophysiology that may not fit the standard model of "single-organ failure" on which the current recommendations for transplantation are based. These patients present with additional risks, such as those with a failing Fontan circulation who are sicker due to protein loosing enteropathy and progressive hepatic and renal dysfunction. The number of possible donors may be limited due to pre-formed antibodies secondary to frequent prior blood transfusions. The majority of patients have had previous cardiovascular surgeries and present technical challenges due to adhesions, altered anatomy, and the presence of vascular collaterals [30–37, 38•]. Although there is no consensus, deteriorating quality of life due to progressive decline in cardiopulmonary function and increased hospital readmissions can be markers for referral and listing [31–36].

A thorough pre-operative workup can guide optimal management. Goerler and colleagues reported their experience with 46 heart-lung and 5 bilateral lung transplants in patients with congenital heart disease and pulmonary hypertension. In the latter group, three patients had congenital cardiac repair performed before HLTx and two at the time of transplantation (one ventricular septal defect closure and one pulmonary artery banding). They reported that previous surgeries increased the post-operative morbidity and mortality and the presence of collaterals provided an additional risk of bleeding. Pre-operative assessment should therefore include detailed imaging with computed tomography to look for important aorto-pulmonary collaterals [31]. Based upon our own experience, failure to delist when patients deteriorate while on the waiting list may explain the majority of our bad outcomes, both with regard to mortality and failure to rehabilitate. Recovery and rehabilitation becomes exceedingly difficult when the patients are too deconditioned pre-operatively and require hospitalization, ventilator support, or ECMO.

Ventilator or Circulatory Support (ECMO) as a Bridge to Heart-Lung Transplant

A significant proportion of patients listed for HLTx are high risk due to progressive decline of cardiac and pulmonary function, which can deteriorate rapidly, requiring extracorporeal support. Although the use of ECMO as a bridge to lung transplantation has become an accepted strategy in patients with end-stage lung disease, its role in patients undergoing HLTx is less defined. Only a few studies have explored the risk vs. benefit of bridge to HLTx. Jarajan et al. analyzed 542 patients who underwent HLTx using the United Network of Organ Sharing database and identified 15 who required ECMO and 22 who required mechanical ventilation prior to HLTx. Each of these two subgroups was then compared to a matched cohort of HLTx patients who were not bridged. Compared to controls, HLTx patients requiring either ECMO or mechanical ventilation had higher mortality on multi-variable analysis ($p < 0.001$ ECMO, $p = 0.030$ mechanical ventilation) and worse 5-year survival ($p < 0.001$ each). On further analysis, the survivors were compared to the non-survivors in each of the subgroups. In the ECMO group, all survivors underwent HLTx 2008 or later, suggesting benefit from increased experience and improved peri-operative management. For both groups, younger age, shorter median ischemic time, and shorter wait list time were associated with better survival ($p < 0.05$ for each), findings consistent with other reported series. In a study by Toyoda et al., combined heart-lung transplant was performed in 17 patients with 5 (29 %) supported with extracorporeal support. Two of these patients were on

ECMO and four had ventricular assist device. Four of the patients were also mechanically ventilated. They reported 100 % survival up to 300 days in these patients and a 1-year survival of 80 %, demonstrating that in selected patients, extracorporeal support can be beneficial and should not be considered a contraindication to HLTx.

A beneficial use of ECMO and/or circulatory support has been supported for the post-operative management of a selected group of patients. Better outcomes may be attributable to a combination of favorable patient-specific factors, such as shorter durations of ECMO/circulatory support, ischemic time, and time spent on wait lists. Our outcomes with both pre- and post-operative ECMO in patients with HLTx were definitely worse than with ECMO support for isolated heart or lung transplantation. Overall, seven patients required pre- or post-operative ECMO before and/or after HLTx and four of these died (60 %). Three required pre-operative ECMO support (two died), two required both pre- and post-operative ECMO (one died), and two required post-operative ECMO (one died).

Benefits of Heart-Lung Transplant in Selected Patients

According to the 31st report of the ISHLT Registry, published in 2014, there has been a 40 % decline in the number of centers performing HLTx since 1994, and the annual rate has stabilized at 62–94 procedures per year in the most recent decade [1••]. HLTx still offers several distinct advantages: (1) it offers survival benefit in patients with severe cardiac dysfunction and complex congenital anomalies with co-existing pulmonary hypertension; (2) although the donor pool is limited, most donors are local so the ischemic times are low, which is also associated with improved outcomes; (3) freedom from BOS-related mortality is superior after HLTx compared to lung transplant alone; (4) it results in significant improvements in cardiac function post-operatively; and (5) the risk of coronary angiopathy is much lower after HLTx compared to heart transplant alone. HLTx also remains the only viable option in selected patients with irreversible advanced cardiac disease in the setting of a pulmonary disease [1••, 2–4, 30–37, 38•, 39]. Like most centers, we only offer HLTx as the very last option, when the possibility of other treatment options has been excluded. We have learned the hard way that the chance of survival and successful rehabilitation following HLTx in patients who are excessively sick and debilitated is lower than after transplantation of other organs.

Summary and Conclusion

Review of our own experience and the literature demonstrates that despite the overall decline in its use over the last few decades, HLTx remains the procedure of choice in carefully selected patients. Although HLTx is non-inferior to bilateral lung transplant in patients with congenital heart disease and idiopathic pulmonary hypertension, HLTx should be reserved to those patients for whom it is the only remaining therapeutic option.

Optimal timing of HLTx varies highly from patient to patient due to adaptation and variable pathology. It is, however, important to identify and list patients before they become too sick. A multi-disciplinary model for managing these complex patients should be implemented and these patients should be monitored closely for progressive deterioration of functional status, in order to be considered for HLTx listing.

In patients with pulmonary hypertension and relatively well-preserved cardiac function, bilateral lung transplant is the preferred technique, but HLTx can be considered in the presence of advanced right and/or left ventricular dysfunction. Patients with right heart failure appear to do better with HLTx, and we have listed a few patients for either double lung or HLTx, should a block become available. In general, preference for HLTx can be given when there is severe left and/or right ventricular dysfunction, the patient has more severe pre-operative disease such as renal or hepatic dysfunction, or there is a need for inotropic support or short-term extracorporeal support.

Acknowledgments This study was supported in part by John and Judy Chew and the Warden Foundation.

Compliance with Ethical Standards

Conflict of Interest Jay J. Idrees and Gösta B. Pettersson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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