ORIGINAL ARTICLE

Double-lung versus heart-lung transplantation for precapillary pulmonary arterial hypertension: a 24-year single-center retrospective study

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SUMMARY

Transplant type for end-stage pulmonary vascular disease remains debatable. We compared recipient outcome after heart-lung (HLT) versus double-lung (DLT) transplantation. Single-center analysis (38 HLT–30 DLT; 1991–2014) for different causes of precapillary pulmonary hypertension (PH): idiopathic (22); heritable (two); drug-induced (nine); hepato-portal (one); connective tissue disease (four); congenital heart disease (CHD) (24); chronic thromboembolic PH (six). HLT decreased from 91.7% [1991–1995] to 21.4% [2010–2014]. Re-intervention for bleeding was higher after HLT; ($P = 0.06$) while primary graft dysfunction grades 2 and 3 occurred more after DLT; ($P < 0.0001$). Graft survival at 90 days, 1, 5, 10, and 15 years was 93%, 83%, 70%, 47%, and 35% for DLT vs. 82%, 74%, 61%, 48%, and 30% for HLT, respectively (log-rank $P = 0.89$). Graft survival improved over time: 100%, 93%, 87%, 72%, and 72% in [2010–2014] vs. 75%, 58%, 42%, 33%, and 33% in [1991–1995], respectively; $P = 0.03$. No difference in chronic lung allograft dysfunction (CLAD)-free survival was observed: 80% & 28% for DLT vs. 75% & 28% for HLT after 5 and 10 years, respectively; $P = 0.49$. Primary graft dysfunction in PH patients was lower after HLT compared to DLT. Nonetheless, overall graft and CLAD-free survival were comparable and improved over time with growing experience. DLT remains our preferred procedure for all forms of precapillary PH, except in patients with complex CHD.

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Key words
chronic thromboembolic pulmonary hypertension, congenital heart disease, Eisenmenger syndrome, lung transplantation, pulmonary arterial hypertension, pulmonary vascular disease

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Introduction

Lung transplantation is the treatment of choice for selected patients with end-stage pulmonary hypertension (PH) refractory to medical or surgical treatment [1]. Among all indications for lung transplantation, PH-recipients have the lowest reported survival rates at 1 year [2]. Heart-lung (HLT), double-lung (DLT), and single-lung (SLT) transplantation have all been reported as effective methods to improve prognosis. There is, however, no consensus in the literature on the best transplant type with regard to postoperative outcomes.

Pulmonary hypertension-patients present with non-specific symptoms and progressive exertional dyspnea. PH may eventually lead to right heart failure and death. Diagnosis of PH requires right heart catheterization as it is defined by a mean pulmonary artery pressure (PAP) ≥25 mmHg at rest [3]. According to the latest classification of the PH World Symposium, patients are categorized into five groups based on common clinical features [4]. Transplantation should be considered in patients when maximal disease-specific medical treatment for PH has failed and in inoperable patients with chronic thromboembolic pulmonary hypertension (CTEPH) or those with persisting PH after pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (AS) [1,5].

Primary graft dysfunction (PGD) is a form of acute lung injury presenting with severe hypoxemia, lung edema, and radiographic pulmonary infiltrates in the first 72 h after lung transplantation. It occurs in up to 30% of the transplanted patients jeopardizing early and late outcome [6]. Patients suffering from PH are at higher risk for developing PGD compared to other transplant indications [7]. Prophylactic extracorporeal life support in the first days after transplantation has recently been advocated to avoid severe PGD [8].

Chronic lung allograft dysfunction (CLAD) was recently introduced as an overarching term covering different phenotypes of dysfunction, including obstructive CLAD (bronchiolitis obliterans syndrome-BOS), restrictive CLAD (restrictive allograft syndrome-RAS), and graft dysfunction resulting from causes not related to chronic rejection [9]. CLAD can be diagnosed if there is a sustained lack of normal graft function after transplantation or a decline in forced expiratory volume in one-second (FEV_1) compared with the best postoperative FEV_1 for a duration of minimum 3 weeks. PGD has been identified as a risk factor for CLAD [6,7].

The aim of this study was to compare early postoperative outcome, overall graft survival (recipient survival free from death or re-transplantation), and CLAD-free survival after DLT versus HLT in patients transplanted at our institution for end-stage precapillary PH. The secondary objective was to compare graft survival with increasing experience over the years.

Methods

Patient cohort and study groups

Approval for the study was given by the Ethics Committee for Research at the University Hospitals Leuven (mp14146).

In this retrospective single-center study, the institutional database was searched for PH-patients transplanted between August 1991 and August 2014 to allow follow-up of at least 3 years. In this period, 829 patients (158 SLT-624 DLT-47 HLT) were transplanted (Fig. 1). We focused on transplant recipients with precapillary PH as classified by the World PH symposium [4] including those in group 1 with idiopathic (1.1), heritable (1.2), or drug-induced (1.3) pulmonary arterial hypertension [PAH], those with connective tissue disease [CTD] (1.4.1), portal PH (1.4.3), or congenital heart disease [CHD] with an intra- or extra-cardiac defect resulting in a right-to-left shunt [Eisenmenger syndrome-ES] (1.4.4), and recipients in group 4 with CTEPH (4.1). Patients with PH secondary to left heart disease (group 2), lung diseases (group 3), or unclear mechanisms (group 5) as well as re-transplants were also excluded from the study.

Seventy PH-patients belonging to group 1 and group 4 were identified. Two patients underwent SLT (one in group 1.3 and 1.4.1 each) and were excluded from the study. Despite initial enthusiasm [10], SLT is no longer advocated for PH-patients because of life-threatening problems when developing PGD or CLAD [1]. The study cohort consisted of 68 PH-recipients diagnosed according to current guidelines. Before transplantation, all patients were treated with pulmonary vasodilators (prostanoid analogues, endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, and/or inhaled NO).

The choice of procedure evolved over time. The first six patients (all CHD) were treated with HLT until April 1994. Thereafter, DLT was progressively performed in selected patients with PAH and CTEPH. HLT was continued as the preferred procedure for all CHD-patients during the entire study period.

Transplant International 2019; 32: 717–729

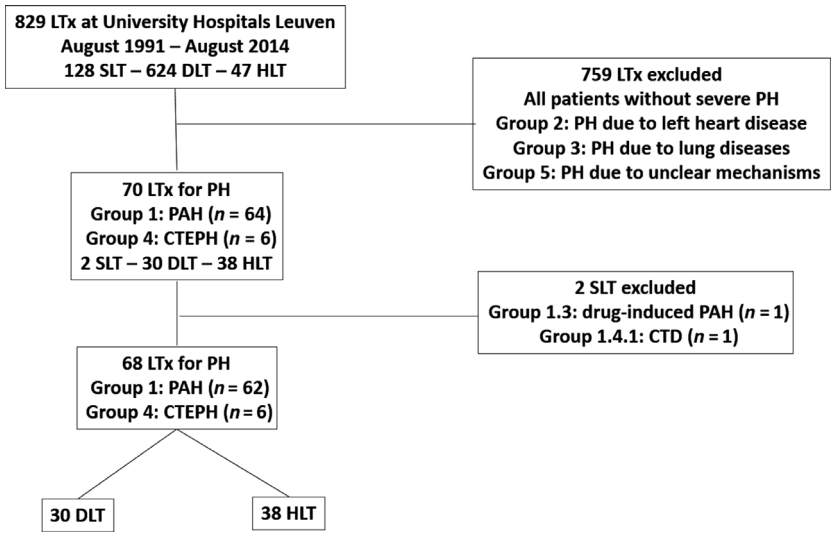

Figure 1 Flow chart with patient selection in the study. CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLT, double-lung transplantation; HLT, heart-lung transplantation; LTx, lung transplantations; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SLT, single-lung transplantation.

Follow-up

No patients were lost to follow-up [median 184 months (41–317)].

After hospital discharge, all recipients were seen in the out-patient clinic whenever indicated and at least three times per year with clinical examination, imaging, biochemistry, pulmonary function, and annual transthoracic echocardiography. Coronary angiography was not routinely performed in HLT patients.

Primary graft dysfunction and CLAD were defined according to the criteria as proposed by the International Society for Heart and Lung Transplantation (ISHLT) [6,9]. Re-transplantation in our center is considered in younger patients developing CLAD and having no other absolute contraindication.

All patients received induction therapy with intravenous (IV) rabbit anti-thymocyte globulin (rATG; 3 mg/kg, qd for 3 days; Fresenius, Bad Homburg, Germany), followed by conventional triple-drug immunosuppression with methylprednisolone, a calcineurin inhibitor (cyclosporine A or tacrolimus) and a cytostatic agent (azathioprine or mycophenolate mofetil) with no differences between HLT versus DLT. Drug choice and dosing adjustments were made according to standardized protocol at the discretion of the treating clinician, based on blood leukocytosis, renal function, trough levels and postoperative period.

Statistics

All patient data were collected and entered into our lung transplant database. Continuous variables are presented as mean ± standard deviation (SD) or as median (minimum-maximum) and were compared using the unpaired, two-tailed *t*-test. Categorical variables are reported as proportion (%) and were compared using the chi-square test. Post-transplantation graft survival and CLAD-free survival were analyzed using the Kaplan-Meier method with no adjustment for any potential confounder. A log-rank test was used to compare survival between HLT and DLT.

All statistical analyses were performed using Prism 5.0. Values of $P < 0.05$ were considered significant.

Results

Transplant type and indication

In this series, 38 HLT and 30 DLT patients were identified (Table 1). Sixty-two were transplanted for PAH including 24 with CHD and six for CTEPH. A gradual shift in transplant type during the study period was noticed with more HLT in the first quintile [1991–1995]: 11/12 = 91.7% and more DLT in the last period [2011–2014]: 11/14 = 78.6% (Fig. 2). Consequently, follow-up was significantly longer after HLT versus DLT [234 (70–317) vs. 113 (41–284) months, respectively; $P < 0.0001$].

Patient and donor demographics

Median age of recipients was 40 years (5–61 years) with DLT recipients being significantly older [47 (15–61) years vs. 37 (5–59) years, respectively; $P = 0.004$] (Table 1). More female patients (42 F/26 M) were transplanted with no gender difference between transplant type ($P = 0.45$).

The indication for transplantation differed significantly between both types because of the exclusive use of HLT

Table 1. Recipient and donor demographics.

	HLT (n = 38)	DLT (n = 30)	P-value
Recipient			
Gender (M/F)	13/25	13/17	0.45
Age (years), median (min–max)	37 (5–59)	47 (15–61)	**0.004**
Diagnosis (PH group)*	(n)	(n)	**<0.0001**
Group 1: PAH	34	28	
Idiopathic (1.1)	5	17	
Heritable (1.2)	1	1	
Drug-induced (1.3)	3	6	
CTD (1.4.1)	0	4	
Portal PH (1.4.3)	1	0	
CHD (1.4.4)	24	0	
Group 4: CTEPH (4.1)	4	2	
Previous thoracic procedures (yes/no)	12/26	1/29	**0.003**
Donor			
Gender (M/F)	11/27	12/18	0.35
Age (years), median (min–max)	34 (9–61)	47 (23–63)	**<0.001**
Ventilation (h), median (min–max)	33 (10–214)	54 (15–321)	**0.007**
PaO_2/FiO_2 (mmHg), median (min–max)	520 (387–697)	484 (218–625)	**0.011**
Ischemic time (min), median (min–max)	259 (112–399)	427 (279–799)†	**<0.0001**

CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLT, double-lung transplantation; F, female; FiO_2, inspired oxygen fraction; HLT, heart-lung transplantation; M, male; PAH, pulmonary arterial hypertension; PaO_2: partial arterial oxygen pressure.

Significant value with $P < 0.05$ (in bold).

*PH group as defined by the PH World Symposium [4].

†Second lung in DLT.

in all CHD-patients. Among six recipients grafted for CTEPH, one patient underwent previous PEA, but needed transplantation later on as a result of persistent PH and right heart failure. For the five remaining recipients with CTEPH, upfront PEA was not an option because of extensive distal disease (n = 4) or a combination with severe COPD (n = 1).

Twelve (31.6%) HLT recipients had a previous thoracic procedure versus one (3.3%) DLT patient only (P = 0.003).

There was a significant difference in donor profile between both groups (Table 1). Not surprisingly, HLT recipients received organs from younger donors ($P < 0.001$) with shorter duration of mechanical ventilation before explantation (P = 0.007), better oxygenation (P = 0.011), and shorter total ischemic time ($P < 0.0001$).

Preoperative variables

No significant differences between transplant types were found for New York Heart Association functional class, systolic PAP, and 6 min walking distance (Table 2). However, HLT patients had a lower cardiac index preoperatively (2.02 ± 0.55 vs. 2.47 ± 0.76 l/min/m^2; P = 0.035).

Waiting period

Median waiting time for HLT recipients appeared longer although this difference failed to reach statistical significance [152 (4–715) vs. 73 (4–683) days; P = 0.26] (Table 2). Transplant waiting times were relatively short because priority was given to listed PH candidates. No candidate was delisted because of a need for extracorporeal support.

Fourteen patients (5 HLT vs. 9 DLT) were bridged to transplantation by balloon AS. None of the patients needed veno-arterial extracorporeal membrane oxygenation (v-a ECMO). Prior to transplantation four patients (2 HLT–2 DLT) were admitted to the intensive care unit (ICU) with three (2 HLT–1 DLT) being ventilated.

Operative technique

Heart-lung transplantation was performed via a midline sternotomy in all (n = 37) except one patient transplanted via bilateral anterior thoracotomy with transverse sternotomy (clamshell incision). For DLT, clamshell incision was the most commonly used surgical approach (n = 20). In the remaining patients (n = 10),

Transplant International 2019; 32: 717–729

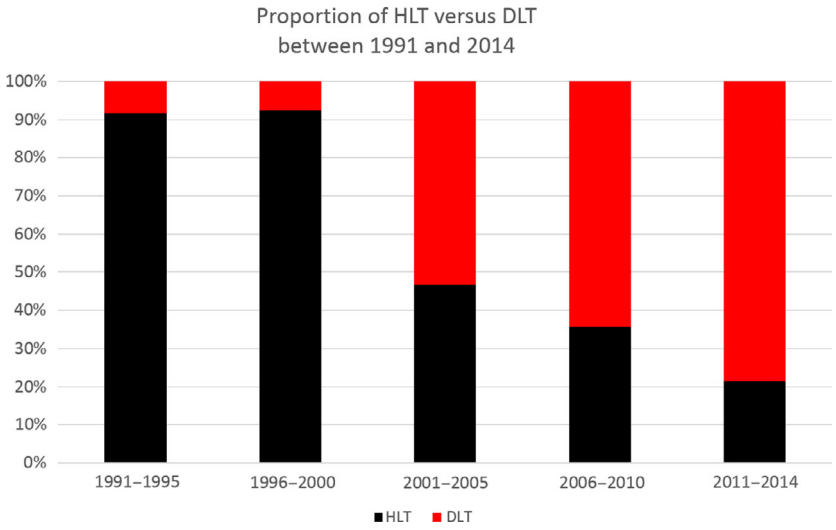

Figure 2 Proportion of heart-lung versus double-lung transplantations for pulmonary hypertension between August 1991 and August 2014 categorized per quintile. DLT, double-lung transplantation; HLT, heart-lung transplantation

Table 2. Preoperative variables.

Preoperative variable	HLT (n = 38)	DLT (n = 30)	P-value
NYHA functional class, mean ± SD	3.42 ± 0.58 (n = 26)	3.33 ± 0.55 (n = 30)	0.55
Cardiac index (l/min/m^2), mean ± SD	2.02 ± 0.55 (n = 19)	2.47 ± 0.76 (n = 26)	**0.035**
Systolic PAP (mmHg), mean ± SD	89.6 ± 24.6 (n = 28)	89.3 ± 27.3 (n = 30)	0.96
6 min walking distance (m), mean ± SD	299 ± 118 (n = 23)	319 ± 133 (n = 30)	0.58
Waiting time (days), median (min–max)	152 (4–715) (n = 38)	73 (4–683) (n = 30)	0.26

DLT, double-lung transplantation; HLT, heart-lung transplantation; NYHA, New York Heart Association; PAP, pulmonary artery pressure.
Significant value with $P < 0.05$ (in bold).

bilateral anterior thoracotomies were applied. All transplants were performed with the aid of extracorporeal life support (ECLS): 48 with cardiopulmonary bypass (CPB; 38 HLT-10 DLT) and 20 DLT with v-a ECMO using either central cannulation (45 CPB and 15 ECMO) or peripheral cannulation via the groin (3 CPB and 5 ECMO); $P = 0.71$.

In none of the DLT recipients, the tricuspid valve was repaired for severe preoperative regurgitation.

Postoperative outcome

Time to extubation as well as length of ICU and total hospital stay did not differ between DLT and HLT (Table 3).

Postoperative medical morbidity was comparable. Twenty-seven patients suffered from an early surgical complication including hemorrhage (n = 17), phrenic nerve paralysis (n = 5), pneumothorax (n = 3) or pleural effusion needing chest tube (n = 1), and wound complications (n = 2) with no significant differences between both groups ($P = 0.25$). Surgical re-intervention in the first postoperative days was necessary in 14 patients, all for postoperative bleeding [11/38 (28.9%) after HLT vs. 3/30 (10.0%) after DLT; $P = 0.06$].

Primary graft dysfunction grades 2 and 3 within the first 72 h after transplantation occurred in 28 out of 51 (54.9%) patients with sufficient data available. DLT recipients were more prone to PGD (76.7% vs. 23.8%; $P < 0.0001$) with three patients needing postoperative veno-venous (v-v) ECMO support, all after DLT.

In-hospital mortality

Overall in-hospital mortality rate was 19.1% (13/68) with no significant difference between HLT (9/38 or 23.7%) and DLT (4/30 or 13.3%); $P = 0.29$ (Table 3).

Late mortality

During follow-up, 25 patients died, 14 related to CLAD with no difference between groups (HLT: 57% vs. DLT:

Table 3. Postoperative outcome.

Postoperative variable	HLT (n = 38)	DLT (n = 30)	P-value
Ventilation (days), median (min–max)	10 (3–52) (n = 18)	10 (2–157) (n = 28)	0.60
ICU LOS (days), median (min–max)	16 (7–89) (n = 18)	16 (3–158) (n = 28)	0.74
Hosp LOS (days), median (min–max)	38 (14–132) (n = 21)	34 (17–325) (n = 26)	0.64
Medical* morbidity, yes/no (%)	13/17 (43.3%)	16/14 (53.3%)	0.45
Surgical complication, yes/no (%)	18/20 (47.4%)	10/20 (33.3%)	0.25
Hemorrhage (n)	12	5	
Phrenic nerve paralysis (n)	4	1	
Hydrothorax – pneumothorax (n)	2	2	
Wound problem (n)	0	2	
Revision for bleeding, yes/no (%)	11/27 (28.9%)	3/27 (10.0%)	0.06
PAH (n)	8	3	
CHD	7		
Portal PH	1		
Idiopathic		2	
Heritable		1	
CTEPH (n)	3		
Chest left open yes/no (%)	5/33 (13.2%)	1/29 (3.3%)	0.16
PGD† Grade 2 and 3 < 72 h, yes/no (%)	5/16 (23.8%)	23/7 (76.7%)	**<0.0001**
Tracheostomy yes/no (%)	2/18 (10%)	8/24 (26.6%)	0.16
ECMO support for PGD, yes/no (%)	0/25 (0%)	3/27 (10%)	0.10
In-hospital mortality, yes/no (%)	9/29 (23.7%)	4/26 (13.3%)	0.29
Cause of death:			
PGD (n)	1	1	
Bleeding (n)	2	1	
Sepsis (n)	1		
Multiple organ failure	2	1	
Invasive aspergillosis		1	
Acute rejection (n)	2		
Right heart failure (n)	1		

CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLT, double-lung transplantation; ECMO, extracorporeal membrane oxygenation; HLT, heart-lung transplantation; Hosp, hospital; ICU, intensive care unit; LOS, length of stay; PAH, pulmonary arterial hypertension; PGD, primary graft dysfunction.

Significant value with $P < 0.05$ (in bold).

*Including kidney failure, liver failure, heart failure, critical illness neuropathy, pneumonia, sepsis, heart rhythm disorders, acute rejection.

†PGD was calculated according to the ISHLT 2005 definition as discussed in the new 2016 consensus publication [6].

55%; $P = 0.90$). Other causes of death were infection ($n = 3$), nonlymphoid malignancy ($n = 2$), acute graft failure ($n = 3$), cardiac arrest ($n = 2$), and unknown ($n = 1$).

Long-term graft survival

Four patients were censored at re-transplantation for graft failure. Median graft survival was 5.9 years: 7.2 years after HLT vs. 5.3 years after DLT. The Kaplan-Meier graft survival curve for all patients is shown in Fig. 3a. Overall survival was 87%, 78%, 65%, 49%, and 31% at 90 days, 1, 5, 10, and 15 years, respectively. No survival difference was observed between HLT versus DLT (82%, 74%, 61%, 48%, and 30% vs. 93%, 83%, 70%, 47%, and 35%, respectively; $P = 0.89$; Fig. 3b).

After excluding deaths within the first postoperative year ($n = 15$), no significant difference in graft survival was seen between HLT ($n = 28$) and DLT ($n = 25$); $P = 0.51$ (Fig. 3c).

Graft survival increased over time when compared per quintile, but the overall difference failed to reach statistical significance ($P = 0.36$; Fig. 3d). However, survival was significantly better for patients transplanted in the period [2011–2014] compared to [1991–1995]: 100%, 93%, 87%, 72%, and 72% vs. 75%, 58%, 42%, 33%, and 33% at 90 days, 1, 5, 10, and 15 years, respectively; $P = 0.03$.

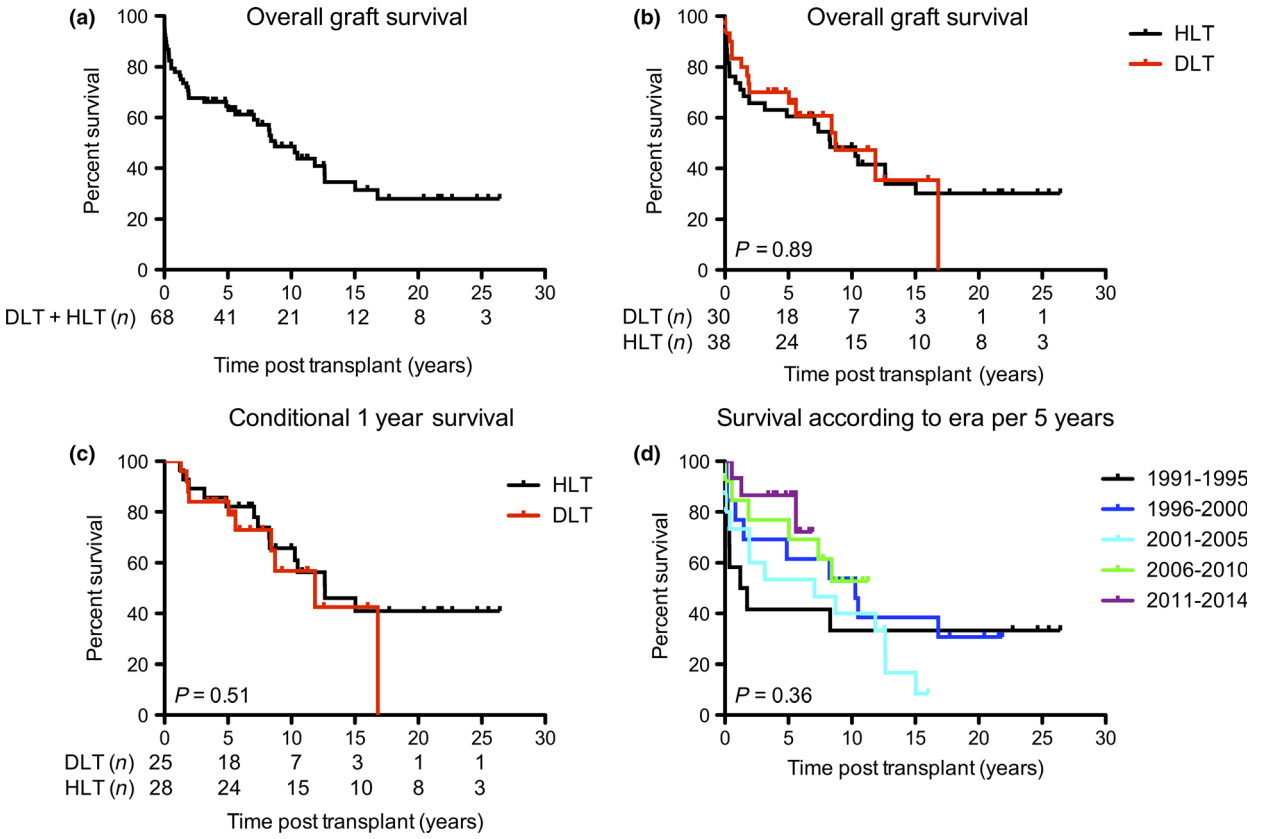

Figure 3 Patient survival free from death or re-transplantation (graft survival). (a) Overall graft survival in 68 patients with precapillary pulmonary hypertension. The proportion of actuarial survival was 87%, 78%, 65%, 49%, and 31% at 90 days, 1, 5, 10, and 15 years, respectively. (b) Graft survival in 38 heart-lung transplant (HLT) vs. 30 double-lung transplant (DLT) recipients. No significant difference was identified between both transplant types. The proportion of actuarial survival was 82%, 74%, 61%, 48%, and 30% for HLT vs. 93%, 83%, 70%, 47%, and 35% for DLT at 90 days, 1, 5, 10, and 15 years, respectively (log-rank $P = 0.89$). (c) Conditional 1-year graft survival in 28 HLT vs. 25 DLT recipients. No significant difference was identified between both transplant types. Conditional 1-year survival was 82%, 66%, and 41% for HLT vs. 84%, 57%, and 43% for DLT at 5, 10, and 15 years, respectively (log-rank $P = 0.51$). (d) Overall graft survival after heart-lung (HLT) or double-lung (DLT) transplantation over time categorized per quintile. No significant difference was identified overall between 5-year cohorts transplanted during the study period [1991–2014] ($P = 0.36$). Graft survival in patients transplanted between [2011–2014], however, was significantly improved when compared to [1991–1995]: 100%, 93%, 87%, 72%, and 72% vs. 75%, 58%, 42%, 33%, and 33% at 90 days, 1, 5, 10, and 15 years after transplantation, respectively; log-rank $P = 0.03$.

CLAD-free survival

In the overall study population, 98% of the patients were free from CLAD after 1 year and 80%, 29%, and 25% after 5, 10, and 15 years, respectively (Fig. 4a). There was no significant difference in CLAD-free survival between HLT versus DLT; $P = 0.49$ (Fig. 4b).

During follow-up, four patients (5.9%) underwent lung re-transplantation for end-stage CLAD (1 redo SLT and 2 redo DLT after HLT vs. 1 redo DLT after DLT). Two of these patients have died since then. In the HLT group, two more patients were listed for redo DLT, but both died prematurely while on the waiting list.

Discussion

Main findings

We report on a single-center retrospective study comparing recipient outcome after HLT versus DLT in patients transplanted for end-stage precapillary PH over a 24-year period. The main findings of our study are that in-hospital mortality, long-term graft survival as well as CLAD-free survival were similar between both study groups. There was a trend for more re-interventions for bleeding after HLT, while PGD was significantly higher after DLT. Overall in-hospital mortality in this high-risk group was 19.1%, but not different between both transplant types. Overall 90-day survival, however, improved from 75% in

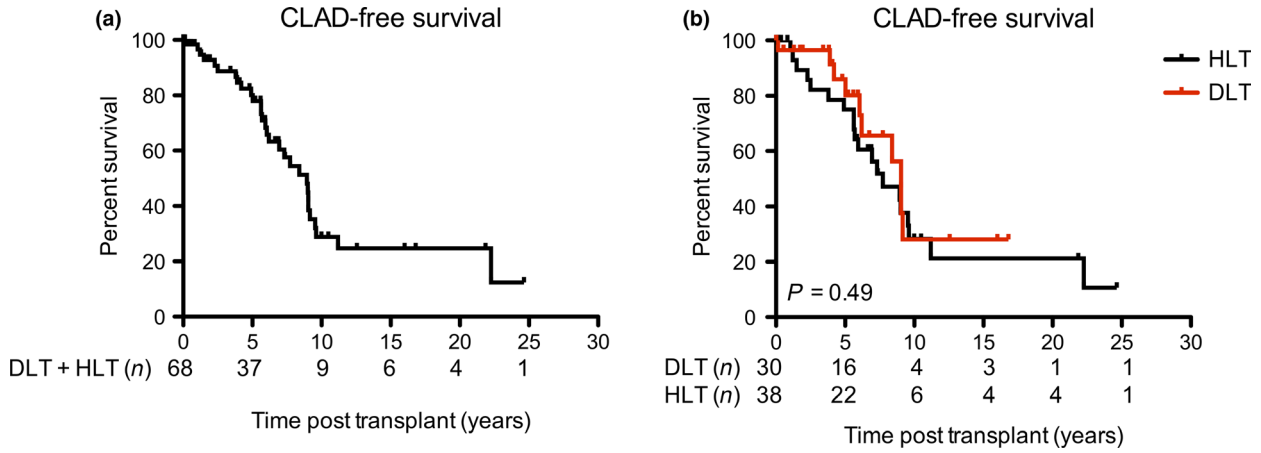

Figure 4 Chronic lung allograft dysfunction (CLAD)-free survival. (a) CLAD-free survival after lung transplantation in 68 patients with precapillary pulmonary hypertension. The proportion of CLAD-free survival was 98%, 80%, 29%, and 25% at 1, 5, 10, and 15 years after transplantation, respectively. (b) CLAD-free survival in 38 heart-lung transplant (HLT) vs. 30 double-lung transplant (DLT) recipients. No significant difference was identified between both transplant types. The proportions of CLAD-free survival were 96%, 75%, 28%, and 21% after HLT vs. 96%, 80%, 28%, and 28% after DLT at 1, 5, 10, and 15 years, respectively (log-rank $P = 0.49$).

1991–1995 to 100% in 2011–2014; $P = 0.03$. This remarkable increase is probably multifactorial with increasing experience in our transplant program. Patient selection, surgical techniques, organ preservation, intra-operative management with the implementation of v-a ECMO, immunosuppressive therapy and infection prophylaxis, and prevention and management of PGD and CLAD have also evolved over time.

Relation to previous findings

The 2016 report from the ISHLT registry showed that lung transplantation for PH has the highest perioperative mortality rate and the lowest 1-year survival rate among other major diagnostic indications with actuarial survival of 78%, 72%, 53%, and 37% after DLT and 77%, 70%, 49%, and 36% after HLT at 90 days, 1, 5, and 10 years, respectively [2]. Survival in our study cohort compares favorably to these international figures. In the subset of patients with idiopathic PAH, a relatively higher proportion of PGD after lung transplantation was also noticed in the ISHLT Registry [2]. A study based on data from the Scientific Registry of Transplant Recipients in the United States reported by Hill *et al.* showed comparable overall survival between HLT and DLT. However, mortality in PAH patients admitted to the intensive care unit prior to transplantation was 1.8-fold higher [11]. We did not observe such a difference in survival in our study ($P = 0.22$).

The results of four published single-center reports comparing HLT versus DLT for PH are summarized in Table 4 [12–15]. When comparing our findings with the largest series published by Fadel *et al.* [12], 5-year graft survival (70% vs. 52% for DLT and 61% vs. 50% for HLT, respectively) and 5-year CLAD-free survival (75% vs. 60% for DLT and 80% vs. 79% for HLT, respectively) were somewhat better in our study.

Similar to our findings, Toyoda *et al.* [13] found significantly better survival in a more recent era in 89 patients receiving either HLT or DLT for PAH [1982–1993; $n = 59$]: 58%, 39%, and 27% vs. [1994–2006; $n = 30$]: 86%, 75%, and 66% at 1, 5, and 10 years, respectively; $P = 0.004$. Also, in the study by de Perrot *et al.* [14], post-transplant 30-day mortality decreased significantly over time [(1997–2004): 24% vs. (2005–2010): 6%; $P = 0.007$], but long-term survival remained unchanged. According to the ISHLT Registry, survival after DLT and HLT in general has also improved over time for all diagnoses [2].

Evolution over time in transplant type for pulmonary vascular disease

During the eighties, HLT was considered the only valid transplant option for patients with end-stage pulmonary vascular disease [16]. Because of the scarcity of high-quality donor hearts and the competition with a growing number of heart transplant candidates on the waiting list, DLT was introduced in the nineties as a viable option for PH-patients with reversible right heart function. Simultaneously, experience with DLT for other indications such as cystic fibrosis and emphysema increased. As a result, the proportion of PH-patients treated with DLT increased gradually over the years

Table 4. Single-center studies comparing heart-lung versus double-lung transplantation in patients with pulmonary hypertension.

First author [Ref] year published city study period	Patients (PH group*)	PGD†	In-hospital mortality	Overall 5-year survival	CLAD-free (BOS-free) survival at 5 years
Fadel *et al.* [12] 2010 Paris 1986–2008	219 patients DLT: 67 HLT: 152 (including 44 patients in groups 3 and 5)	DLT: 49% HLT: 32% $P = 0.012$	DLT: 14.9% HLT: 21.7% $P = 0.24$	DLT: 52% HLT: 50% $P = 0.932$	DLT: 70% HLT: 84% $P = 0.035$
Toyoda *et al.* [13] 2008 Pittsburgh 1982–2006	80 patients DLT: 31 HLT: 49 (patients with IPAH in group 1 only)	NS	NS	DLT: 64% HLT: 40% $P = 0.655$	NS
de Perrot *et al.* [14] 2012 Toronto 1997–2010	79 patients DLT: 57 HLT: 22 (all patients in groups 1 or 4)	NS	NS	Reported as being "similar" $P = 0.7$	NS
Ueno *et al.* [15] 2000 Melbourne 1990–1997	35 patients DLT: 13 HLT: 22 (all patients in group 1 + 2 patients in group 3)	Reported as "no difference in PO_2/FiO_2 at 24 h"; $P = 0.44$	DLT: 0% HLT: 9% $P = 0.52$	Survival up to 2 years only $P = 0.93$	NS
Current study 2019 Leuven 1991–2014	68 patients DLT: 30 HLT: 38 (patients in groups 1 and 4 only)	DLT: 77% HLT: 24% $P < 0.0001$ (grade 2 and 3 within 72 h)	DLT: 13.3% HLT: 23.7% $P = 0.29$	DLT: 70% HLT: 61% $P = 0.89$	DLT: 80% HLT: 75% $P = 0.49$

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; DLT, double-lung transplantation; HLT, heart-lung transplantation; IPAH, idiopathic pulmonary arterial hypertension; NS, results not stated in paper; PGD, primary graft dysfunction; [Ref], reference.

*According to the World Symposium on pulmonary hypertension [4].

†PGD was calculated according to the ISHLT 2005 definition as discussed in the new 2016 consensus publication [6].

resulting in a decline in HLT [2]. Pharmacological management of PH has also improved over time and patients are now being listed for transplantation later in the course of their disease [3–5].

All CHD-patients at our institution were treated with HLT, while the transplant type for patients with other forms of PAH or CTEPH gradually shifted from HLT to DLT over the years. Of notice, in the study by Toyoda *et al.* [13], the proportion of HLT also decreased over time from 69.5% to 26.7% comparable with the decrease in our program from 91.7% to 21.4% in the first versus the latest 5-year cohort. Other groups have reported successful DLT in patients with ES with simultaneous repair of the cardiac defect. In a study by Waddell *et al.* [17] based on ISHLT Registry data (1988–1998), survival in 605 ES-patients was compared between HLT and DLT. In general, for all types of cardiac defects, HLT resulted in better survival in comparison to DLT, especially for the subgroup with ventricular septal defect (VSD) compared to atrial septal defect (ASD) and patent ductus arteriosus. The survival difference seemed to occur mostly in the first 30 days post-transplant, suggesting that the surgery and the early postoperative care in patients with VSD can be more challenging after DLT. The authors therefore concluded that HLT should remain the procedure of choice for ES-patients with VSD often in combination with another complex cardiac anomaly. On the other hand, in a small single-center study with 35 patients, Ueno and colleagues concluded that DLT for ES can be performed as an alternative procedure to HLT without an increase in early and medium-term morbidity and mortality [15].

Pathophysiologic changes after DLT for PH

In addition to endothelial ischemia-reperfusion injury, both right (RV) and left (LV) ventricular dysfunction after DLT for PH may play a role in the development of PGD as a result of acute hemodynamic changes in afterload and preload, respectively.

Immediately after DLT, the hypertrophied RV faces a substantial decrease in PVR and initially still ejects blood with high pressures into the new pulmonary vasculature. This might lead to pulmonary overflow and reperfusion injury with PGD. Notably, right heart remodeling occurs shortly after DLT [18] and preoperative RV dysfunction does not limit long-term survival [11,12].

New-onset LV dysfunction early after DLT in PH-recipients has also been described by several authors [19–22]. In patients with severe long-standing PH, the LV is often chronically volume-deprived, and as such, small, stiff, and dysfunctional. In this situation, the LV is not always capable of handling the increase in preload immediately after transplantation. Postoperative LV remodeling occurs in most of the patients, but it takes time. Weaning from mechanical ventilation causes stress and an increased afterload for the fragile LV, making it the most vulnerable period to develop LV dysfunction and respiratory failure. To avoid transient LV dysfunction and subsequent cardiogenic edema, our DLT patients were sedated and mechanically ventilated for at least 48–72 h after transplantation to allow the LV to adapt to the increased preload, with cautious weaning afterwards.

Several groups with Vienna being the first, have reported the use of prolonged, prophylactic v-a ECMO during the first postoperative days [8]. The Hannover group has subsequently published their experience with prolonged ECMO for 5 days allowing early weaning and extubation while still on v-a ECMO and thus facilitating early ambulation and avoiding muscle deconditioning and ventilator-associated lung infections [23]. These authors recently published their experience in 38 patients with decreased postoperative mortality compared to previous results in these higher-risk patients with PH [24].

Bridge to lung transplantation for pulmonary vascular disease

On top of their chronic right heart decompensation, PH-patients while on the waiting list may acutely deteriorate before a suitable donor organ becomes available. Possible triggers can be progressive intolerance to vasodilator therapy or a new-onset infection. Several ECLS modes have been described to bridge these patients towards urgent lung transplantation [25]. These include v-a ECMO in various configurations [26], pulmonary artery-to-left atrium pumpless interventional lung assist device [27], and balloon AS combined with or without v-v ECMO for better oxygenation [28]. In our study population, AS was performed in 14 patients with severe and persistent right heart failure refractory to maximal therapy [29]. AS has been suggested as a possible therapy to train the chronically deprived LV prior to transplantation [30]. No consensus, however, exists about the size of the septostomy as well as the timing to perform this procedure, neither whether the opening should be closed at the time of transplantation or later on during the postoperative course when still indicated [19].

Current transplant strategy for PH at University Hospitals Leuven

Our initial research question whether long-term survival in patients with end-stage PH differs between HLT versus DLT remains unanswered. We continue to prefer DLT in patients with PAH and CTEPH, because of the critical donor heart shortage and longer waiting times for a transplantable heart-lung bloc. Moreover, the dilated and dysfunctional RV in many PH-patients most likely remodels after DLT. In our experience, the increased rate of PGD observed in DL recipients did not pose a serious problem and did not result in a higher incidence of CLAD in the later course. The exact reasons remain speculative. We believe that PGD in DLT patients is more related to cardiogenic edema (transsudate) rather than inflammatory edema (exsudate) rapidly resolving after stabilization of hemodynamic status. In fact in our entire program ($n > 1000$ procedures), we cannot find an association between PGD and CLAD.

So far, all CHD-patients in our institution were listed for HLT because of the underlying cardiac defect regardless of the potential of myocardial function to recover after transplantation. Noteworthy, in patients with CHD and previous surgical interventions, a higher incidence of postoperative bleeding can be expected. Parenchymal blood supply is increased via pleural arterial collaterals that can bleed significantly when taking down adhesions. In addition, profound coagulopathy as a results of aggressive anticoagulation for the use of CPB during HLT may occur more often in contrast to DLT patients transplanted on v-a ECMO. In selected CHD-patients therefore a more customized approach may need to be considered in the future with DLT in patients with repairable defects and potential for RV remodeling. Our first DLT in a patient with ES with closure of a pre-existing ASD was successfully performed in 2017. In addition, HL recipients are exposed to the risk of developing cardiac graft vasculopathy that may ultimately result in late death from myocardial infarction in long survivors. This happened to one patient in our series.

Nowadays, HLT is performed under standard CPB with central cannulation via sternotomy or clamshell. For DLT, we prefer central v-a ECMO through a right thoracotomy or clamshell if not possible otherwise. In case of severe right heart dysfunction preoperatively, ECMO cannulas are inserted via the femoral vessels prior to induction of anesthesia.

Limitations and strengths

Our study is flawed by several limitations. First, it is a retrospective single-center analysis with a small study population over a long time. Our study therefore may be underpowered to detect statistically significant differences. In addition, postoperative variables including blood gases to calculate PGD scores and need for tracheostomy were sometimes missing in the ICU medical records. Measured echocardiographic data on right ventricular enlargement and dysfunction, the presence of ascites and kidney dysfunction that may all have influenced the choice between HLT versus DLT, could no longer be retrieved. Second, the indication for HLT has changed over time resulting in an imbalance in the transplant type with more DLT performed in the second half of the study period. Increasing surgical experience and techniques, improved immunosuppression and infection prophylaxis, earlier recognition and better management of PGD over time may have influenced our results differently between HLT versus DLT. Third, patients after HLT had longer follow-up and were consequently more at risk to develop CLAD-related death. Finally, analysis of possible risk factors and risk-adjusted survival was not performed. Because of the limited number of cases with similar transplant indication, no propensity score matching analysis could be performed between HLT and DLT to reduce the potential selection bias.

The strength of our study, however, lies in the length of the follow-up as well as the fact that all patients were followed at our own center. All recipients were thereby subjected to the same treatment regime appropriate at that time. Moreover, we only studied patients from groups 1 and 4 with precapillary PH excluding those with secondary PH related to other causes as included in other larger series [12].

Unfortunately, a prospective, randomized study comparing HLT versus DLT for end-stage PH is no longer possible nowadays because of ethical constraints for optimal utilization of scarce young donor hearts. There will always be a bias in the distribution of transplant types for PH according to underlying diagnosis. Further multicenter studies are needed to investigate which transplant type is best in these complex patients and to analyze risk factors influencing survival, PGD, and CLAD.

Conclusions

We did not find any significant difference in early mortality, overall graft survival, and CLAD-free survival between HLT and DLT. There was a trend for more re-interventions for bleeding after HLT, while PGD was more frequent, but manageable after DLT. Graft survival in this high-risk group of PH-patients has improved significantly over time with growing experience.

Authorship

JB and DVR: were responsible for the conception and design of the work. JB, SEV, RQ and DVR: performed the data collection. JB, SEV and DVR: did the data analysis and interpretation of the obtained results. JB and DVR: wrote the article. SEV, TV, FR, MVDV, GP, SR, AN, GVDB, DV, WB, RV, CB, MD and GMV: did a critical revision of the article. TV, WC, HD, PDL, LD, PN, HVV, BM, FR, MVDV, GP, SR, AN, GVDB, DV, JVC, WB, RV, CB, MD, GMV and DVR: were involved in overall clinical management of patients included in the present study. All authors have read and approved the submitted manuscript.

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Conflicts of interest

The authors have declared no conflict of interest.

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