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Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome

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Abstract

OBJECTIVES: Lung transplantation for idiopathic pulmonary arterial hypertension has the highest reported postoperative mortality of all indications. Reasons lie in the complexity of treatment of these patients and the frequent occurrence of postoperative left ventricular failure. Transplantation on intraoperative extracorporeal membrane oxygenation support instead of cardiopulmonary bypass and even more the prolongation of extracorporeal membrane oxygenation into the postoperative period helps to overcome these problems. We reviewed our experience with this concept.

METHODS: All patients undergoing bilateral lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative extracorporeal membrane oxygenation with or without prophylactic extracorporeal membrane oxygenation prolongation into the postoperative period between January 2000 and December 2014 were retrospectively analysed.

RESULTS: Forty-one patients entered the study. Venoarterial extracorporeal membrane oxygenation support was prolonged into the postoperative period for a median of 2.5 days (range 1–40). Ninety-day, 1-, 3- and 5-year survival rates for the patient collective were 92.7%, 90.2%, 87.4% and 87.4%, respectively. When compared with 31 patients with idiopathic pulmonary arterial hypertension transplanted in the same period of time without prolongation of extracorporeal membrane oxygenation into the postoperative period, the results compared favourably (83.9%, 77.4%, 77.4%, and 77.4%; $P = 0.189$). Furthermore, these results are among the best results ever reported for this particularly difficult patient population.

CONCLUSIONS: Bilateral lung transplantation for idiopathic pulmonary arterial hypertension with intraoperative venoarterial extracorporeal membrane oxygenation support seems to provide superior outcome compared with the results reported about the use of cardiopulmonary bypass. Prophylactic prolongation of venoarterial extracorporeal membrane oxygenation into the early postoperative period provides stable postoperative conditions and seems to further improve the results.

Keywords: Lung transplantation • Extracorporeal membrane oxygenation • Idiopathic pulmonary arterial hypertension

INTRODUCTION

Results of lung transplantation (LuTX) have improved significantly over time and especially perioperative mortality has significantly diminished. However, among the different indications for LuTX, idiopathic pulmonary arterial hypertension (iPAH) or non-operable chronic thromboembolic pulmonary arterial hypertension has until recently owned the highest perioperative mortality [1], whereas

survival after LuTX conditional on survival to 3 months for iPAH patients is among the best. This strongly suggests that the long-term outcome of iPAH patients mainly depends on problems occurring around the transplantation and not on the indication itself. Several reasons for this phenomenon can be identified; among them are the pronounced comorbidity of these patients and especially the complexity of the immediate pathophysiological changes occurring after LuTX, which typically results in a challenging postoperative treatment. Traditionally, transplantation of patients with iPAH has always been performed with the intraoperative use of cardiopulmonary bypass (CPB). A more recent approach is the intraoperative use of extracorporeal membrane oxygenation (ECMO) instead of CPB [2, 3] and even more, its planned prophylactic prolongation into the early postoperative period, which owns a number of advantages and allows overcoming the aforementioned problems. In this article, we review our institutional experience with this concept in patients with iPAH undergoing bilateral LuTX (BLTX) over a time period of 15 years.

MATERIALS AND METHODS

A retrospective analysis of all patients undergoing BLTX for iPAH at the Medical University Vienna between January 2000 and December 2014 transplanted on intraoperative ECMO support with or without prolongation into the postoperative period was performed.

Demographic data

A total of 72 patients entered the study. There were 31 patients with intraoperative ECMO only and 41 patients with intraoperative ECMO that was prophylactically prolonged into the postoperative period. There was no difference between the 2 cohorts of patients in basic patient characteristics such as age, female to male ratio, weight and body mass index (Table 1). Serum creatinine and creatinine clearance did not differ, and there was no significant difference in the number of patients with clinically significant ascites (defined as ascites that necessitated intraoperative drainage). In 35% of the patients, pericardial effusions were detected by transthoracic echocardiography at the time of listing.

However, a number of differences were calculated for other factors. Mean systolic pulmonary artery pressure measured at the time of BLTX was significantly higher in patients with prolonged ECMO compared with patients with intraoperative ECMO only ($P = 0.044$). Two patients in the prolonged ECMO cohort were bridged to BLTX with venoarterial (v/a) femoro-femoral ECMO (bridging time: Patient 1: 11 days—after resuscitation for right heart failure; Patient 2: 2 days), whereas none was bridged in the intraoperative ECMO only cohort. A significantly higher percentage of patients in the prolonged ECMO group were on a triple drug combination therapy ($P = 0.012$). A significantly higher percentage of patients in Group B presented with New York Heart Association (NYHA) Stage IV ($P = 0.036$). See also Table 1 for more details.

In addition, a clear difference over time was observed for the number of patients with intraoperative ECMO only and those with intraoperative plus prolonged ECMO. During the early experience, ECMO was only prolonged in case of need for aggressive ventilation, high pulmonary artery pressures and haemodynamic instability. Later on, ECMO prolongation became the routine treatment strategy. As a matter of fact, more patients from the recent cohort belonged to the prolonged ECMO cohort (Fig. 1).

Follow-up was complete. The median follow-up time was 1825 days (minimum 5/maximum 1825).

Bilateral lung transplantation technique, type of transplantation and immunosuppression

Donor lungs were harvested during multi-organ procurement preserved with colloid containing low potassium solution (Perfadex®) and kept inflated during transport. None of the

Table 1: Basic demographic data

	ECMO intraoperative	ECMO intraoperative + prolonged	*P*-value
n	31	41	
Age, years (mean ± SD)	31.9 ± 12.4	33.4 ± 11.6	0.594
Female:male ratio, *n* (%)	18:13 (58.1:41.9)	31:10 (75.6:24.4)	0.114
Body weight, kg [median (range)]	64 (19–93)	57 (20–100)	0.342
Body mass index, kg/m^2 (mean ± SD)	21.6 ± 4.6	20.6 ± 3.5	0.329
PAPsys, mmHg (mean ± SD)	102.0 ± 26.3	116.8 ± 29.2	**0.044**
PH-specific triple drug therapy, *n* (%)	5 (16.1)	15 (36.6)	**0.012**
Ascites[a] (mean ± SD)	8 (25.8)	11 (26.8)	0.922
Prostaglandin pump, *n* (%)	18 (58.1)	23 (56.1)	0.392
Creatinine, mg/dl (mean ± SD)	1.1 ± 0.3	0.98 ± 0.46	0.195
Creatinine clearance, ml/min (mean ± SD)	65.3 ± 24.7	61.9 ± 24.2	0.780
NYHA Stage, *n* (%)			
III	14 (45.2)	9 (22.0)	**0.036**
IV	17 (54.8)	32 (78.0)	
BLTX type, *n* (%)			
BLTX	22 (71.0)	15 (36.6)	
BLTX size reduced	4 (12.9)	14 (34.1)	
BLTX lobar	4 (12.9)	11 (26.8)	
Split lung	1 (3.2)	1 (2.4)	

ECMO: extracorporteal membrane oxygenation; PAP_{sys}: systemic pulmonary arterial pressure; PH: pulmonary hypertension; NYHA: New York Heart Association; BLTX: bilateral lung transplantation.

[a]Ascites that was drained intraoperatively.

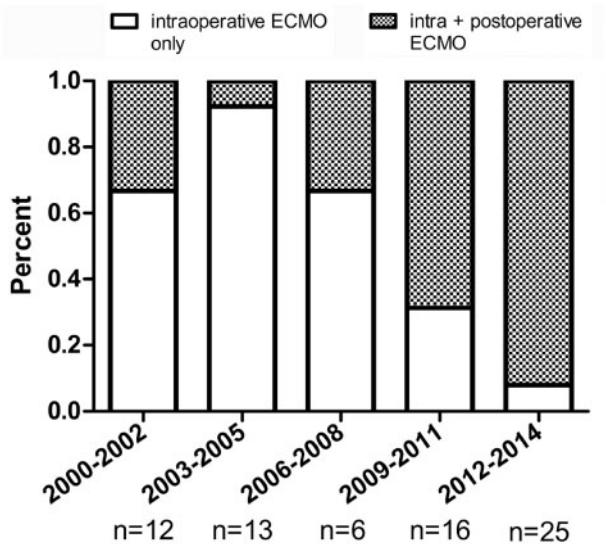

Figure 1: Use of different modes of ECMO (1 January 2000–31 December 2014). Histogram displaying the use of prophylactic postoperative ECMO in patients with iPAH undergoing BLTX (3-year intervals). ECMO: extracorporteal membrane oxygenation; iPAH: idiopathic pulmonary arterial hypertension; BLTX: bilateral lung transplantation.

patients in this study received a lung conditioned with *ex vivo* lung perfusion. BLTX was performed in standard technique through bilateral thoracotomy or clamshell incision. Grafts were flushed in retrograde and antegrade ways. The following types of LuTX on intraoperative ECMO with prolongation into the postoperative period were performed: BLTX ($n = 15$, 36.6%), size reduced BLTX ($n = 14$, 34.1%), split LuTX ($n = 1$, 2.4%) and lobar BLTX ($n = 11$, 26.8%; Table 1). For whole lung transplants, the total lung capacity predicted ratio between donors and recipients (D/pR index) was close to 1.0.

Basic immunosuppression consisted of a triple drug regimen with cyclosporine (or tacrolimus), mycophenolate mofetil and corticosteroids. Anti-thymocyte globulin or alemtuzumab (Campath) were used for induction therapy.

Extracorporeal membrane oxygenation management

All patients were transplanted on intraoperative v/a ECMO (heparin-bound ECMO (Medtronic Carmeda®), hollow-fibre oxygenator (Medtronic), centrifugal pump (Biomedicus®), flow probes and 3/8-inch internal diameter heparin-bound tubing). In the majority of the patients, central cannulation of the ascending aorta with a 22-Fr curved tip or straight tip cannula (Medtronic) and single 2-stage cannulation of the right atrium was used. Some patients had peripheral cannulation in the groin, mainly when severe haemodynamic instability made immediate and direct installation of circulatory support necessary during induction of anaesthesia. Central cannulation provides better venous drainage as well as physiologic antegrade flow to the coronary arteries and aortic arch with great vessels. Transoesophageal echocardiography was installed in all patients to monitor cardiac function intraoperatively.

In patients with 'prolonged ECMO', ECMO was switched prophylactically from its central location to peripheral cannulation after implantation of the lungs. For postoperative v/a ECMO prolongation, patients were cannulated in the groin and the intraoperatively used ECMO device was connected. Cannula size was carefully selected not to compromise distal femoral artery flow (15–17 Fr cannula for femoral artery and 17–19 Fr cannula for the femoral vein). In case of small arterial diameter or occlusion of the artery by the cannula, separate cannulation for distal limb perfusion was installed (6–10 Fr). Anticoagulation during prolonged ECMO support was managed by either continuous heparin perfusion (activated partial thromboplastin time 50–60 s) or subcutaneous administration of low-molecular-weight heparin. Continuous monitoring of oxygen saturation at the right upper extremity and on the cannulated lower limb was performed. A Swan-Ganz catheter was used to measure pulmonary artery pressures. ECMO flow was kept at a low level, usually representing half of the normal cardiac output. Special care was taken to maintain a pulsatile pulmonary artery flow while reducing mean pulmonary artery pressure as much as possible. Fraction of inspired oxygen was kept 100% at ECMO initiation. Partial pressure of carbon dioxide was maintained in the range of 30–40 mmHg by altering sweep gas flow.

Echocardiography is part of the postoperative routine to assess cardiac function. Mostly transthoracic echocardiography is used to monitor adequacy of fluid management and adrenergic support.

ECMO remained in place until patients were haemodynamically stable, had normal chest X-ray, adequate oxygenation (fraction of inspired oxygen <0.5), low ventilation pattern and most importantly were normalized with their fluid balance, i.e. excessive fluid load was removed (oedema, ascites). At that point of time, pump flow was continuously decreased to 1.2–1.5 l/min, and after a short tryout period, ECMO was discontinued. Piperazillin/tazobactam was administered routinely for antibiotic prophylaxis. In cases of longer periods of ECMO prolongation, antifungal prophylaxis was added.

Patients with postoperatively prolonged ECMO received mechanical ventilation throughout and beyond ECMO support with a protective low tidal volume pattern.

Normalization of fluid balance had a high degree of priority in the postoperative management strategy. Since all patients were already on preoperative diuretic medication, intravenous diuretic therapy, either in continuous way or as bolus therapy, was administered after the transplantation. If this turned out to be inadequate to achieve negative fluid balance and normalization of fluid homeostasis, temporary haemofiltration was applied.

Definition of primary graft dysfunction

According to the definition of primary graft dysfunction (PGD) by the ISHLT, patients on postoperative ECMO are automatically Grade 3 regardless of the functional status of the lung [4]. To study 'early graft dysfunction' in the prophylactic ECMO group, we defined PGD in patients on postoperatively prolonged ECMO as infiltrates indicating reperfusion oedema on chest X-ray within the first 72 h after transplantation as no gas exchange without ECMO was determined in these patients.

Statistical methods

Statistical analysis of data was performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. IBM Corp., Armonk, NY, USA). Graphical methods (histograms) were employed to test normality. Data were reported as mean ± standard deviation for normally distributed

Table 2: Postoperative data

	ECMO intraoperative ($n = 31$)	ECMO intraoperative + prolonged ($n = 41$)	P-value
PGD Grade, *n* (%)			
0	14 (45.1)		
1	4 (12.9)		
2	5 (16.1)		
3	8 (25.8)		
PGD (CXR only) yes:no, *n* (%)		8:33 (19.5:80.5)	
ECMO postop, days	1 patient, 4 days	2.5 (1–40)	
Haemofiltration, *n* (%)	14 (45.2)	17 (41.5)	0.754
Tracheostomy, *n* (%)	14 (50)	24 (58.5)	0.484
Length of ventilation, days [median (range)]	8 (1–41)	10 (1–90)	0.611
ICU stay, days [median (range)]	18 (1–89)	19.5 (3–125)	0.260
Hospital stay, days [median (range)]	35 (1–143)	36.0 (5–145)	0.550

ECMO: extracorporteal membrane oxygenation; PGD: primary graft dysfunction; ICU: intensive care unit.

data and median (range) for non-normal distributions. Unpaired Student's *t*-test was used to compare means of 2 independent groups with normal (Gaussian) distributions. Non-parametric Wilcoxon rank-sum test was used when the assumption of normality or equal variances was not met. The χ^2 test for independence was used for analysis of frequencies in 2 or more groups (e.g. sex differences). The probability of making a Type I error was set at an α value of 0.05. The null hypothesis was rejected if the P-value was less than α. Two-tailed P-values were employed. Kaplan–Meier survival analysis was used to assess outcome measures: overall survival (end point of interest:death of any cause). Log-rank test was used to assess statistical differences between different subgroups. GraphPad Prism (GraphPad Prism, version 6.00 for Windows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com) was used for graphical display of all box plots, Kaplan–Meier curves and correlations in this article.

Ethics statement

Ethics approval was obtained from the Medical University Vienna review board on human research.

RESULTS

There were no major intraoperative complications. Patients were transferred to the intensive care unit (ICU) and stayed on prolonged v/a inguinal ECMO for a median of 2.5 (range 1–40) days. Patients with prolonged ECMO were ventilated for a median of 10 (range 1–90) days; stayed at the ICU 19.5 (range 3–125) days and in the hospital for 36 (range 5–145) days (Table 2 compares patients with and without prolonged ECMO). Length of ICU stay was frequently determined by the need for temporary haemofiltration.

Mortality

Patients with prolonged extracorporeal membrane oxygenation. Perioperative (30-day) mortality was 2.4%. The only patient who died on the 5th postoperative day was due to cardiopulmonary failure. In this patient, ECMO had been removed on the 4th postoperative day at a time where retrospectively seen his condition was not yet optimized.

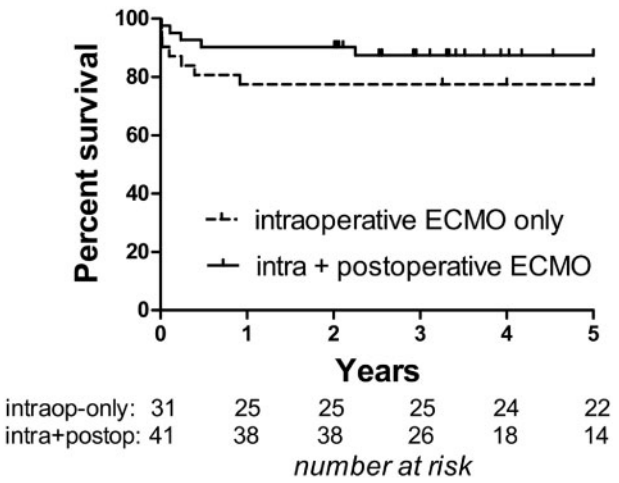

Figure 2: Survival depending on the use of prolonged ECMO. Patients with intraoperative ECMO with prolongation into the postoperative period were compared with a historic control group with intraoperative ECMO only. ECMO: extracorporteal membrane oxygenation.

A total of 4 late deaths occurred due to multi-organ failure (40th and 86th postoperative days) and chronic lung allograft dysfunction (CLAD) (822nd and 3882nd postoperative days), respectively.

This mortality resulted in a 90-day, 1-, 3- and 5-year survival rate of 92.7%, 90.2%, 87.4% and 87.4%, respectively (Fig. 2).

Patients with intraoperative extracorporeal membrane oxygenation only. There were 3 perioperative deaths in patients without prolonged ECMO support. The causes of death were attributed to bleeding (on the day of surgery) and graft failure (6th and 7th postoperative days). Five deaths were observed in patients without prolonged ECMO due to sepsis (postoperative Days 37, 89, 143 and 335, respectively) and 1 death due to CLAD on postoperative Day 1928.

General morbidity and extracorporeal membrane oxygenation-related complications

Postoperative complications in patients with prolonged ECMO occurred in 17 patients (41.4%) in total and included revision

Table 3: Complications related to ECMO

n (%)	17 (41.4)
Rethoracotomy for bleeding	7 (17.1)
ECMO-related	
Infection at cannulation site in groin	1 (2.4)
Thrombosis of leg cannula	2 (4.9)
Possibly ECMO-related	
Symptomatic transitory psychotic syndrome	4 (9.7)
Radiological signs of subarachnoidal bleeding[a]	2 (4.9)
Hypoxic brain damage	1 (2.4)

Patients with iPAH undergoing BLTX on intraoperative ECMO with prolongation into the postoperative period.

ECMO: extracorporteal membrane oxygenation; iPAH: idiopathic pulmonary arterial hypertension; BLTX: bilateral lung transplantation.

[a]Radiological signs of subarachnoidal bleeding on otherwise inconspicuous cranial computed tomography scans, in particular no signs for compression of the brain.

surgery for haemorrhage, neurological complications and local problems resulting from the ECMO insertion in the groin (Table 3).

Need for haemofiltration and need for tracheostomy (Table 2) were not considered as complications but rather as part of the strategy to treat this advanced disease. However, temporary haemofiltration was applied in 41.5% of patients (Table 2). Duration of haemofiltration was 22.4 ± 19.9 days. None of the patients experienced irreversible renal damage requiring permanent haemodialysis or renal transplantation. Median serum creatinine and median blood urea nitrogen at the time of discharge from the hospital was 0.7 (range 0.29–9.33) mg/dl and 20.2 (range 5.6–76.7) mg/dl, respectively.

Primary graft dysfunction in patients with or without prolonged extracorporeal membrane oxygenation support

Patients supported solely by intraoperative ECMO developed PGD in 54.8% (for PGD grades, see Table 2). In comparison, patients with prolonged ECMO support showed signs of mild radiological changes (18.9% PGD), but none of these patients developed severe reperfusion oedema (Table 2 and Methods for PGD definitions).

Functional outcome

At 6 months after BLTX, all patients had improved to NYHA Class I or II. No difference between the 2 groups was calculated: intraoperative ECMO only: NYHA Class I 85.2% and NYHA Class II 14.8% versus intraoperative ECMO with prolongation into the postoperative period: NYHA Class I 81.6% and NYHA Class II 18.4% ($P = 0.702$).

Freedom from CLAD at 1, 3 and 5 years was 94.6%, 81.9% and 76.5% for patients with prolonged ECMO and 95.8%, 77.6% and 68.1% for patients with intraoperative ECMO only, respectively (Fig. 2). There were no statistically significant differences in freedom from CLAD between patients with or without prolonged ECMO support ($P = 0.798$; Fig. 3).

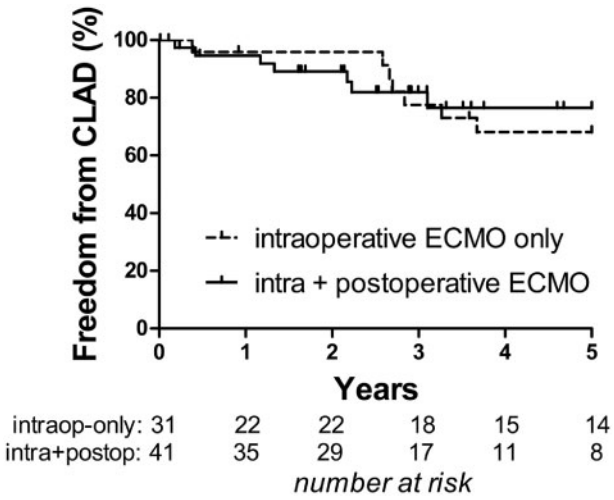

Figure 3: Freedom from CLAD in iPAH patients undergoing BLTX on intraoperative ECMO with prolongation into the postoperative period compared to intraoperative ECMO support only. CLAD: chronic lung allograft dysfunction; ECMO: extracorporteal membrane oxygenation; iPAH: idiopathic pulmonary arterial hypertension; BLTX: bilateral lung transplantation.

Comparison with patient group transplanted without prolonged extracorporeal membrane oxygenation

At all time points, survival rates were better in the prolonged ECMO group: 92.7% vs 83.9% at 90 days, 90.2% vs 77.4% at 1 year, 87.4% vs 77.4% at 3 years and 87.4% vs 77.4% at 5 years, respectively, although these differences did not reach statistical significance ($P = 0.189$) (Fig. 2).

Mortality in patients without postoperatively prolonged extracorporeal membrane oxygenation

There were 3 perioperative deaths without prolonged ECMO support. The causes of death were attributed to bleeding (on the day of surgery) and graft failure (6th and 7th postoperative days). Furthermore, there were 5 late deaths due to sepsis (postoperative Days 37, 89, 143 and 335, respectively) and 1 death due to CLAD on postoperative Day 1928.

DISCUSSION

Survival at 1 year after LuTX for iPAH is around 72%, according to ISHLT registry data, which in fact identifies PAH as the indication with the highest early postoperative mortality [1]. However, if survival conditional on survival to 3 months is considered, results turn around completely and iPAH [as well as cystic fibrosis (CF)] are the indications with the best 1-year as well as 5-year survival. This gives clear evidence that limitations in long-term outcome in iPAH patients undergoing LuTX mainly depend on poor results during the immediate postoperative period. This finding is even more remarkable, since LuTX for iPAH is technically much easier than for several other groups of indications. In fact, the main problems of LuTX for iPAH can be found in the combination of pronounced comorbidity and a challenging perioperative management based on unique and specific pathophysiologic mechanisms.

The pattern of comorbidities that can be found in patients coming to LuTX with advanced iPAH consists of impaired renal function with severe fluid retention despite maximal diuretic therapy, resulting leg oedema and ascites formation, impaired hepatic function due to congestion and sometimes thrombocytopathy due to continuous prostaglandin therapy. Although all these problems can be reversed after LuTX, it takes time until normalization can occur, and consequently, management of the patients during the perioperative period remains complex.

Besides these general problems, transplantation of patients with iPAH has unique pathophysiological impact on cardiac function, which is not seen in any other patient group. Patients with severe iPAH have a chronically underfilled left ventricle, which is highly reduced in its dimensions and stroke volume. The typical echocardiographic picture is the so-called 'banana-shaped' left ventricle with severe bulging of the septum towards the left. Implantation of lungs with normal pulmonary vascular resistance results in dramatic increase of cardiac output and increased filling of the left ventricle. Not infrequently, the untrained left ventricle cannot handle this increased volume load immediately, which can lead to temporary left ventricular failure [5]. Although classical reperfusion oedema and PGD are seen immediately after implantation of the lungs, this special situation occurs at a time point when cardiac inflow is increased, which is during weaning and around extubation (Table 4—lung transplantation for pulmonary hypertension: haemodynamic effects, resulting problems and postoperative strategies). The strategy to overcome this phenomenon consists of reduction of fluid load, increase of inotropy and most importantly in providing the left ventricle time to adapt to the new pathophysiologic conditions. Forced diuresis/haemofiltration, application of inotropic medication and delayed extubation are therefore the cornerstones of postoperative management, however, sometimes are not sufficient alone to provide stable postoperative conditions. An even more effective method of temporary reduction of cardiac output represents postoperatively prolonged v/a ECMO, which bypasses a considerable part of the cardiac output from the heart and lungs. In fact, the reduction of flow through the heart/lung system represents the main advantage of postoperatively prolonged v/a ECMO, besides the fact that it provides general haemodynamic stability. Prolonged v/a ECMO reduces cardiac output, lowers pulmonary artery pressure and therefore reduces reperfusion injury to the lungs, which in summary could be seen as an optimal prolonged controlled reperfusion [6]. It also allows ventilating patients with a very smooth and protective ventilation pattern (low tidal volumes and plateau pressures), which avoids secondary damage to the lungs by the otherwise frequently required aggressive ventilation techniques [7].

However, in rare cases with severe hypertrophy of the right ventricular wall, a decreased filling volume of the right ventricle based on excessive fluid reduction can lead to muscular right ventricular outflow tract obstruction. To identify such a situation, repeated echocardiographic monitoring is mandatory (Table 4) [8].

In fact, ECMO has meanwhile replaced CPB as the standard intraoperative support technique in many departments (Vienna [3], Hannover [9], Munich [10], Toronto [11], Pittsburgh [12] and CUMC New York [13]). In our institution, we have introduced the strategy of LuTX on intraoperative ECMO support as early as 2000 and a large experience with more than 130 transplantations on ECMO was already reported in 2007 [14]. ECMO has several advantages over the use of CPB, since it only requires low heparinization, which avoids the need for suction of blood and consequent activation of platelets [13]. Especially in iPAH patients, who typically present with the before mentioned coagulation problems, this becomes an important factor. Early in our experience with this concept, we started to continue ECMO support into the postoperative period whenever immediate graft function was not satisfying. Soon we realized that prolongation of ECMO into the early postoperative period provides optimal controlled reperfusion conditions to the lung and therefore could be of special value in patients with iPAH. Results of this strategy were described in 2002 in an article by Pereszlenyi *et al*. [3] from our group. In this publication, we reported about 17 patients with different forms of severe pulmonary hypertension (PH) who were transplanted with this concept with a 90-day mortality as low as 5.5% (1 patient). As a consequence of these very reassuring results, the strategy of prolonging intraoperative ECMO into the postoperative period became the standard of treatment in our department for this particular group of patients.

One of the management goals is the smooth weaning of patients from mechanical ventilation. To mobilize patients early (when extubation is not yet possible), we are very liberal with the

Table 4: Lung transplantation for pulmonary hypertension

Effects	Problems	Time	Strategy	Rationale
Reduction of PVR > increase of CO	Overflow of TX lung	Immediately after LTX	BLTX Fluid restriction/PEEP Prolonged use of v/a ECMO	Provide large pulmonary vascular bed Keep circulatory flow rate low Relieve pulmonary circulation from total CO
Reduction of RV size	RV outflow tract obstruction (in cases of muscular hypertrophy)	During weaning	Increase in circulatory volume Avoidance of beta-agonists	Normalize RV filling
Normalization of septal position > normalization of LV filling	Temporary LV failure	During weaning	Diuretic therapy haemofiltration Beta-agonists Prolonged ventilation	Normalize fluid balance Increase inotropy of LV Provide LV sufficient time for adaptation

Haemodynamic effects, resulting problems and postoperative strategies, with permission from ISHLT monograph series editor James K. Kirklin [8].
BLTX: bilateral lung transplantation; ECMO: extracorporeal membrane oxygenation; CO: cardiac output; LV: left ventricle; LTX: lung transplantation; RV: right ventricle; PEEP: positive end-expiratory pressure; PVR: pulmonary vascular resistance; TX: transplantation; v/a: venoarterial.

indication for percutaneous or surgical tracheostomy in this patient collective. We do not consider tracheostomy a complication, but it is rather a part of the management strategy.

The frequency of ECMO-related complications of the described patient cohort of lung transplant recipients is low compared with complications reported for the treatment of other indications [15]. There was only 1 infection at the cannulation site that was treated by negative pressure wound therapy and thrombosis of 2 leg cannulas that were exchanged. The use of ECMO may have caused other complications that were reported: there were 7 rethoracotomies for bleeding (evacuation of haematoma) and 1 patient with hypoxic brain damage. In patients with symptomatic transitory psychotic syndrome or the 2 patients with radiological signs of subarachnoidal bleeding full recovery was observed.

The intention of this study was to describe a very homogenous patient population and therefore only patients with iPAH were included. Patients with any other form of severe PH, such as inoperable chronic thromboembolic pulmonary arterial hypertension, secondary PH in patients with CF or idiopathic pulmonary fibrosis (IPF), as well as patients with PH in combination with other cardiac defects, were excluded.

The results presented in this article compare very favourably to earlier reports about outcome of iPAH patients after BLTX (Table 5) [1, 16–21]. Latest ISHLT registry data from 2015 report a 3-month survival rate of 78% and a 1- and 5-year survival rate of 72% and 52% for a total of 1550 patients undergoing LuTX for iPAH [1]. Results from larger institutions such as Paris Marie Lannelongue [16], Pittsburgh [17], Toronto [18] and historical results from Hannover [19] range between 52% and 79% 1-year and 35% and 64% 5-year survival rates. All these patients had been transplanted with a traditional management concept without the use of intraoperative or postoperatively prolonged ECMO.

The only reported results that are in a comparable range with this report come from a recent publication of the Hannover group, which followed a very similar concept of postoperatively prolonged ECMO in the most recent years [20]. They reported about 23 patients with severe PH, with the difference to the concept described here, that patients were first weaned from ventilation and only thereafter from ECMO. The 1-year survival of 94% that they achieved with this strategy was almost identical with the here reported 92.7% and the fact that 2 independent groups now report similar good results with the strategy of prolongation of ECMO gives very strong evidence about the particular value of this approach. However, the median time of ECMO support in the Hannover patient group was 8 days (range 5–19 days), whereas duration of ventilation was 3 days (range 0.6–42 days) only, compared with median 2.5 (range 1–40 days) ECMO support and median 10 (range 1–90) days of ventilation in our group of patients. This leads to the discussion, whether weaning from ECMO or weaning from ventilation first, should be preferred. A strong argument for weaning from ECMO first is the potential morbidity that can result from an extracorporeal support system, which in our opinion exceeds the one of pulmonary ventilation after transplantation with a protective ventilation pattern by far. Whatever strategy might be the best, it remains obvious that results of these 2 independent works, both prolonging ECMO postoperatively, are by far the best ever reported for this difficult patient population. This underlines the special value of the here described strategy and also brings its possible use in other patient groups into discussion.

In fact, we have adapted the use of prolonged ECMO support after LuTX in suboptimally performing donor lungs in our department since several years, which resulted in remarkable low PGD rates.

Some other details of the treatment strategies in this particular group of patients are of importance. Especially the use of temporary haemofiltration in 42–45% of patients is quite high compared with other patient populations. However, a large number of iPAH patients comes with already significantly impaired renal function to the transplantation and are unable to clear excessive fluid load by themselves. Fast and efficient reduction of excessive volume load in the immediate postoperative period represents one cornerstone of the treatment concept. In the presence of an already impaired kidney function and sometimes maximal diuretic therapy this cannot be achieved by further forcing diuresis alone. Haemofiltration was initiated to allow negative fluid balances in fluid-overloaded patients in cases where the fluid

Table 5: Reported outcomes of BLTX for iPAH

Society/institution	BLTX (*n*)	Diagnosis	Era	% Survival				
				30 days	90 days	1 year	3 years	5 years
ISHLT [1]	1550[a]	iPAH	1990–2012	83	78	72	60	52
Paris [15]	67	PH	1986–2008	85		79		52
St Louis [20]	19	iPAH	1991–2009			95	73[b]	61
Vienna [3]	17	PH	1999–2001		100	93	93	93
Pittsburgh [16]	31	iPAH	1982–2006			77		64
Toronto [17]	38[c]	iPAH 34	1997–2010	87		73[b]	49[b]	49[b]
Hannover [18]	28[d]	iPAH 29	1988–1998			52	40	35
Hannover [19]	23[e]	iPAH 17	2005–2013		100	94	n.r.	n.r.

Selected lung transplant centres and ISHLT registry. If the results for iPAH were not available, data for other diagnoses were listed (PH, PAH) [1, 3, 15–20].
iPAH: idiopathic pulmonary arterial hypertension; BLTX: bilateral lung transplantation; n.r.: not reported.
[a]ISHLT adult lung transplants 1995–2014: 7% single lung transplants for iPAH.
[b]Survival rates were estimated from the respective article's Kaplan–Meier plots.
[c]Survival data represent patients with severe pulmonary hypertension, including pulmonary veno-occlusive disease (*n* = 3) and 3 sarcoidosis (*n* = 3).
[d]Including heart–lung transplantation (*n* = 14).
[e]Including heart–lung transplantation (*n* = 4).

balance cannot be normalized by pharmacologic treatment. Haemofiltration also had an impact on the length of ICU stay in some patients, but it is important to stress that all patients regained normal kidney function again.

Similarly, weaning of iPAH patients from respiratory support should, in contrast to other indications, be performed very slowly and only after normalization of the patient's fluid load. Even small details, such as positioning of the patient—elevating the upper body—are important at this time. Finally, it is of importance to provide inotropic support not only over the whole period of the weaning process but also even beyond, and frequent monitoring of left ventricular function by echocardiography is essential to guide the therapy [8].

It certainly would have been desirable to compare these results, achieved with ECMO prolongation, in a prospective randomized trial; however, it is obvious that it is almost impossible to do this and to find a perfectly matched patient cohort for comparison. We therefore at least compared the results with the cohort of patients transplanted in the same period of time, which had generally similar management but no prolongation of ECMO into the postoperative period. Still there remained a clear bias between the 2 groups, since especially in the early period of time; preferentially, the sicker patients received ECMO prolongation, whereas only later on, this became the standard treatment for all patients. Despite the fact that this resulted in a higher number of more advanced patients in the ECMO prolongation group, outcome parameters were clearly better at all time points of follow-up, when compared with the group of patients that had no prolongation of ECMO. Although statistical significance was not achieved, it is suggestive that, with a higher number of equally matched patients, it would have also been possible to demonstrate statistical superiority.

Limitations

The retrospective nature of this study is one of its weaknesses. The long study period necessary for collecting this large cohort of iPAH patients undergoing lung transplantation is another limitation of the study. Innovations in diagnostic and therapeutic modalities change treatment practices (e.g. there were more patients with PH-specific triple drug therapy in later time period; referral for lung transplantation: patients in the later time period had higher pulmonary artery pressures).

CONCLUSION

In conclusion, this experience gives evidence that LuTX of patients with severe iPAH with intraoperative ECMO prolonged into the postoperative period provides the best ever reported outcome and therefore should be considered the standard of care for this difficult to treat group of patients.

Conflict of interest: none declared.

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