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Impact of preoperative right-ventricular function and platelet transfusion on outcome after lung transplantation☆

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Abstract

Objective: Lung transplantation has become an established treatment option for end-stage pulmonary diseases. However, outcome depends on preoperative condition and co-morbidity. Furthermore, perioperative blood-product use is known to be associated with worse outcome even in transplant surgery. We investigated the impact of poor preoperative right-ventricular function and blood-product use on outcome after lung transplantation. **Methods:** The medical records of 169 lung-transplant recipients from 1996 to 2006 were examined. Duration of hospital stay, hours on mechanical ventilation, duration of stay in the intensive care unit, perioperative complications, death during hospital stay, and long-term survival were recorded. These outcome parameters were analyzed regarding coherence with right-ventricular function and the perioperative administration of crystalloids, colloids, allogeneic red blood cells, fresh frozen plasma, and platelets. **Results:** Patients with poor preoperative right-ventricular function had a significant increase in postoperative hours on ventilation ($p = 0.005$), intensive care stay ($p = 0.003$), and in-hospital death ($p = 0.012$). The hours on ventilation increased also with high intra-operative fluid administration ($p = 0.026$). Blood-product use was associated with prolonged mechanical ventilation and intensive care stay. After multivariate analysis, transfusion of platelets ($p = 0.022$) was an independent prognostic factor for in-hospital death. Hours of mechanical ventilation was the only independent prognostic factor for long-term mortality ($p = 0.014$). **Conclusions:** Perioperative transfusion of platelets is an independent prognostic factor for perioperative mortality. Furthermore, the study indicated that poor preoperative right-ventricular function might worsen perioperatively after lung transplantation. Therefore, pre-transplant treatment of pulmonary hypertension to protract right-ventricular failure and a restrictive use of allogeneic blood products may be options to improve outcome.

Keywords: Lung transplantation; Hypertension; Pulmonary; Blood platelets; Ventricular function; Right

1. Introduction

Almost 3 decades have passed since the first successful clinical lung transplant was performed in 1983. Over the intervening years, lung transplantation has become the preferred treatment option for a variety of end-stage pulmonary diseases. Remarkable progress has been made in the field through refinement of surgical technique and enhanced understanding of transplant immunology and microbiology, improved intensive post-transplant patient care and advancement of anesthetic and critical-care management. However, outcome is different for different indications and co-morbidity [1]. There were several patients with poor preoperative right-ventricular function (PRVF) and fatal outcome in our lung-transplant program [2]. PRVF has not been studied under this perspective, which disposed us to investigate the impact of PRVF on perioperative outcome in lung transplantation. Perioperative blood-product use is known to be associated with worse outcome after general, cardiac, trauma and liver transplant surgery [3—6]. We, therefore, also investigated the impact of blood-product use in lung transplantation.

2. Methods

Ethical Committee approval was obtained for an anonymized data acquisition. The medical records of all lung-transplant recipients from 1996 to 2006 were examined. The following outcome parameters were recorded: duration of hospital stay, hours on mechanical ventilation, duration of stay in the intensive care unit

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(ICU), perioperative complications including death during hospital stay and long-term mortality. These outcome parameters were correlated with poor versus good PRVF, and perioperative fluid and blood-product administration, that is, Ringer's lactate solution, hydroxyethyl starch, gelatin solution, allogeneic red blood cells (RBCs), fresh frozen plasma (FFP) and platelets. Between 1996 and 2006, blood component therapy at our institution was according to the American Society of Anesthesiologists (ASA) guidelines, that is, in situations of massive bleeding, RBCs were given at hemoglobin concentrations between 6 g dl^{-1} and 10 g dl^{-1}, FFP at prothrombin time (PT) or partial thromboplastin time (PTT) >1.5 times normal and platelets between 50 and 100×10^9 l^{-1} [7]. All echocardiographic studies were performed by a specially trained cardiologist. The studies of all lung-transplant candidates were inspected and corrected at best by the head of the echocardiography lab. Prior to the year 2000, right-ventricular function had been described only by a qualitative report (sufficient or poor function). Thereafter, tricuspid annular motion (TAM) and fractional area change (fac) have been introduced in echocardiography as validated indicators for right-ventricular function. The cut-off values for poor right-ventricular function were TAM ≤17 mm; fac ≤25%. Patients with incomplete data were excluded.

3. Statistical analysis

All outcome parameters have been tested for significant correlation with poor or good right-ventricular function and with perioperative fluid and blood-product administration. Hours on ventilation, intensive care stay and hospital stay have been analyzed with the Mann–Whitney *U*-Test, and perioperative complications and death with Fisher's exact test. All outcome parameters with significance $p \leq 0.07$ for univariate analyses have been further tested for independent impact with stepwise logistic regression. Long-term survival was analyzed using Kaplan–Meier curves. Groups were compared using the log-rank test. Multivariate analysis was performed using stepwise Cox regression. To evaluate the use of cardiopulmonary bypass (CPB) as a possible confounding factor, we analyzed the impact of CPB on in-hospital and long-term survival and on platelet administration.

4. Results

As many as 44 of 213 patients were excluded due to incompleteness of essential data. The medical records of 169 patients were analyzed. Patient characteristics are shown in Table 1. Emphysema, parenchymal lung diseases and cystic fibrosis were the most frequent diagnoses or indications for lung transplantation. A total of 19 patients died during hospital stay and seven had severe complications. Table 2 summarizes perioperative complications. Table 3 shows absolute numbers of in-hospital survivors and deaths relating to the investigated risk factors.

Table 1. Patient characteristics and preoperative diagnosis.

Age (year/range)	42 ± 16/12;68
Height (cm/range)	168 ± 10/133;191
Weight (kg/range)	57 ± 16/24;122
Gender (m/f)	92/77
Pre-mPAP (mm Hg/range)	31 ± 14/10;74
Post-mPAP (mm Hg/range)	22 ± 6/6;40
EMP, *n* (%)	87 (51)
PLD, *n* (%)	36 (21)
CF, *n* (%)	32 (19)
PH, *n* (%)	10 (6)
OTH, *n* (%)	4 (3)

Values are mean ± SD. Pre-mPP: preoperative mean pulmonary artery pressure after anesthesia induction; post-mPP: immediate postoperative mean pulmonary artery pressure prior to the transfer to the ICU; preoperative diagnosis – EMP: emphysema; PLD: parenchymal lung disorders; CF: cystic fibrosis; PH: primary pulmonary hypertension; OTH: other diseases.

5. Univariate analyses

Patients with poor PRVF had significantly augmented postoperative ventilation time ($p = 0.005$), prolonged intensive care stay ($p = 0.003$) and higher risk of in-hospital death ($p = 0.012$). Patients with greater total intra-operative fluid volume administration, that is, blood products, crystalloids and colloids, were longer on mechanical ventilation ($p = 0.026$). However, the individual administration of Ringer's lactate solution, hydroxyethyl starch and gelatin solution showed no significant effect. Last but not the least, blood-product use, that is, use of RBCs, FFP or platelets was associated with a significantly prolonged ventilation time and intensive care stay (Table 4). The use of CPB had no significant impact on in-hospital and long-term survival. The duration of CPB and the total amount of the heparin dose given during bypass were similar in those patients who received platelets and those who did not. The length of CPB and the dose of heparin had no impact on platelet administration (Table 5).

6. Multivariate analyses

Intra-operative transfusion of platelets ($p = 0.022$) was an independent prognostic factor for death during hospital stay, whereas poor PRVF barely missed statistical significance ($p = 0.053$; Table 4). Hours of ventilation was the only independent prognostic factor for long-term mortality ($p = 0.014$), whereas platelet transfusion and poor PRVF

Table 2. In-hospital death and complications.

Death[a], *n* (%)	19 (11)
Severe bacterial infection, *n* (%)	3 (2)
Seropneumothorax, *n* (%)	1 (0.6)
Dehiscent sternum, *n* (%)	1 (0.6)
Encephalopathy, *n* (%)	1 (0.6)
Muscular weakness, *n* (%)	1 (0.6)

Quantity and sort of complications and occurrence of death during the hospital stay.

[a] Causes of in-hospital death (*n*): multi-organ failure (2), multi-organ failure with preceding right heart failure (2), hyperammonemia (3), sepsis (3), right heart failure (2), cerebrovascular lesion (2), esophageal perforation (1), duodenal and colorectal perforation (1), unknown (3).

Table 3. Prognostic factors related to in-hospital survivors and deaths.

Total	In-hospital	In-hospital survivors	Deaths
Poor PRVF	14/150[a] (8%)	9/131[a] (7%)	5/17[a] (29%)
PRBC	113/169 (67%)	96/148 (65%)	15/19 (79%)
FFP	102/169 (60%)	86/148 (58%)	14/19 (74%)
Platelets	20/169 (12%)	13/148 (9%)	6/19 (32%)
TFV	5.3/0;22.8	5.0/0;22.8	6.0/0;21.2
HOV	14/4;5208	12/4;1488	32/6;5208

PRVF: preoperative right-ventricular function.
[a] Data of 19 patients not analyzable due to incomplete preoperative echocardiographic report. PBRC: packed red blood cells; FFP: fresh frozen plasma; TFV: total intra-operative fluid volume, including all blood products, crystalloids and colloids: liters, median/range; HOV: hours of mechanical ventilation: median/range.

were not significant (Figs. 1 and 2). None of the other univariate correlations remained statistically significant in the stepwise logistic regression (Table 4).

Table 4. Univariate and multivariate analysis.

Univariate analysis		Multivariate analysis	
Outcome parameter	*p*-value	*p*-value	OR and HR* (95% CI)
Poor PRVF			
HOV	0.005	ns	
Intensive care stay	0.003	ns	
Hospital stay	ns		
Complications	ns		
In-hospital survival	0.012	0.053 (ns)	4.0 (0.98–16.4)
Long-term survival	ns		
PRBC			
HOV	0.030	ns	
Intensive care stay	0.038	ns	
Hospital stay	ns		
Complications	ns		
In-hospital survival	ns		
Long-term survival	ns		
FFP			
HOV	0.001	ns	
Intensive care stay	0.003	ns	
Hospital stay	ns		
Complications	ns		
In-hospital survival	0.036	ns	
Long-term survival	ns		
Platelets			
HOV	<0.001	ns	
Intensive care stay	0.005	ns	
Hospital stay	ns		
Complications	ns		
In-hospital survival	0.003	0.022	4.5 (1.25–16.3)
Long-term survival	0.054 (ns)	ns	
TFV			
HOV	0.026	ns	
Intensive care stay	ns		
Hospital stay	ns		
Complications	ns		
In-hospital survival	ns		
Long-term survival	ns		
HOV			
Long-term survival	0.026	0.014	1.9* (1.14–3.2)

PRVF: preoperative right-ventricular function; PBRC: packed red blood cells; FFP: fresh frozen plasma; TFV: total intra-operative fluid volume, including all blood products, crystalloids and colloids; HOV: hours of mechanical ventilation; OR: odds ratio; HR: hazard ratio after stepwise Cox regression; CI: confidence interval. All outcome parameters with statistical significance $p \leq 0.07$ for univariate analyses have been further analyzed with stepwise logistic regression to show independent impact. Long-term survival was analyzed using Kaplan–Meier curves. ns: not significant ($p > 0.05$).

Table 5. Impact of cardiopulmonary bypass on survival and platelet administration.

	No CPB	CPB	*p*-value
In-hospital deaths	10/114 (9%)	9/50 (18%)	0.089
5-year survival rate	0.71 ± 0.04	0.64 ± 0.07	0.55
	In-hospital survivors	In-hospital deaths	*p*-value
Duration of CPB[a]	188 (81–390)	189 (81–297)	0.84
Heparin[b]	11250 (3000–27600)	14000 (3500–21600)	0.86
	No platelets	Platelets	*p*-value
No CPB (*n*)	110	5	–
CPB (*n*)	36	15	–
Duration of CPB[a]	186 (81–390)	210 (81–358)	0.25
Heparin[b]	11500 (3000–27600)	16800 (3750–32000)	0.36

CPB: cardiopulmonary bypass. 5-year survival rate: estimate ± standard error.
[a] Duration of cardiopulmonary bypass: minutes (range).
[b] Heparin: units (range).

7. Discussion

In times of organ shortage, risk factors for poor outcome are important indicators, which may have an impact on both the evaluation process of the transplant candidate and the treatment concepts during the time on the waiting list. This study indicates that poor PRVF may be an independent risk factor for fatal outcome, which confirms our impression from clinical practice. Preoperative pulmonary hypertension increases mortality after lung, but also heart, kidney and liver transplantation [1,8–10]. This applies not only for lung-transplant recipients with primary pulmonary hypertension, but also for patients with other indications for lung transplantation such as idiopathic pulmonary fibrosis and cystic fibrosis [11,12]. This corresponds to the experience of our and other lung-transplant programs [2,13,14]. Chronic pulmonary hypertension leads to right-ventricular failure in the majority of cases, even though specific treatment may prolong this process [15]. Therefore, and with regard to the study results concerning poor PRVF, the treatment of

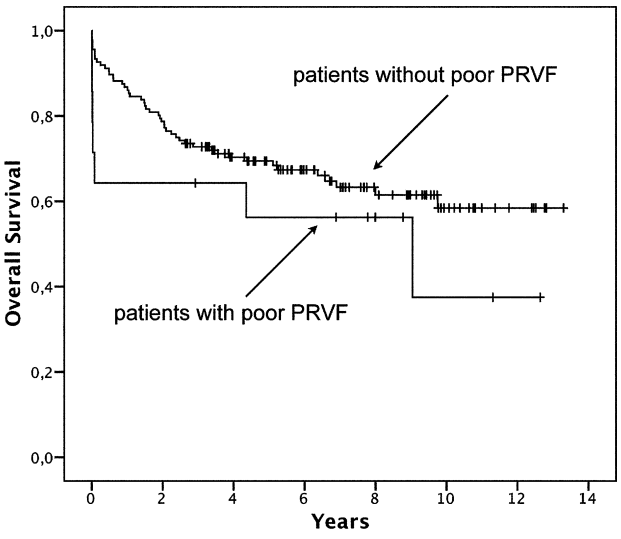

Fig. 1. Cumulative survival of lung transplant patients with or without poor preoperative right-ventricular function (PRVF).

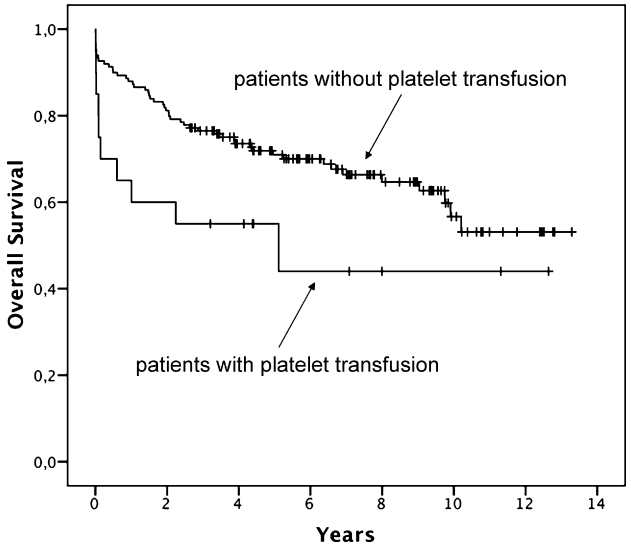

Fig. 2. Cumulative survival of lung transplant patients with or without platelet transfusion.

pulmonary hypertension during the time on the waiting list should be considered as an option to delay the development of right-ventricular failure, which may improve outcome. Several cases where pulmonary hypertension was successfully treated have been published in liver transplantation [16,17]. Although the pathogenesis and classification of pulmonary hypertension may be different for liver and lung transplantation and the therapeutic options and probabilities of success may differ [18], there is no evidence by now, that treatment of pulmonary hypertension in lung-transplantation candidates may not improve perioperative outcome. However, the results of this study should be confirmed with further preferably prospective, randomized and controlled investigations.

This study additionally shows that the transfusion of platelets is correlated with significantly compromised survival during hospital stay. This may seem unexpected at first sight, all the more so as transfusion of FFP and RBCs are known for this adverse effect [19], but have not shown similar impact in lung transplantation. However, our findings are consistent with those of Spiess et al., who showed that platelet transfusion in the perioperative period of coronary artery bypass graft (CABG) surgery is associated with increased risk for serious adverse events such as infection, stroke and death [20]. However, why did only platelets and not also FFP or RBCs have this effect? The reason remained unclear, as it is in our study. The design of their study, similar to ours, was not randomized and controlled. By contrast, McGrath et al. and Karkouti et al. found no increased risk after platelet transfusion in cardiac surgery [21,22]. These studies, as well, were only observational and were neither randomized nor controlled. However, a prospective, controlled study with or without blood-product use is difficult to perform. A multicenter study from Mangano et al. of aspirin use and mortality after CABG surgery showed that platelet transfusion was significantly correlated with a six-fold increase in mortality. Mortality was reduced in patients, who received aspirin [23]. A further study of surgical ICU patients with and without thrombocytopenia reported that although platelet transfusion failed to restore a normal platelet count, thrombocytopenia, and, presumably, platelet transfusion were associated with increased mortality [24]. Last but not the least, Pereboom et al. and other groups showed that platelet transfusion is an independent risk factor for survival after orthotopic liver transplantation due to platelet transfusion-related lung injury [5]. Lung-transplant recipients might be at a similar risk, even though there are different medical and procedural premises in liver and lung transplantation. We also evaluated the use of CPB as a relevant and possibly confounding factor for survival and platelet administration [25]. The analysis did not show a significant correlation. Thus, in view of the current literature and the results of the present study, platelet transfusion should be administered restrictively in lung transplantation.

We also analyzed long-term mortality and found the duration of mechanical ventilation to be the only independent prognostic factor. However, we do not consider the duration of mechanical ventilation causal for mortality because weaning lung-transplant patients was attempted on a daily basis, postoperatively. It is more likely that the most severely ill were mechanically ventilated the longest, some until death.

In summary, this study revealed platelet transfusion as a significant and independent marker for perioperative mortality, which supports the restricted and targeted use of platelet transfusion in lung transplantation. Furthermore, the study indicates that poor PRVF may compromise survival after lung transplantation and preoperative treatment of pulmonary hypertension to protract right-ventricular failure may be a valuable option to improve outcome. These findings need to be validated in randomized and controlled studies.

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