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Transplant & Mechanical Support: Research

The Effect of Prone Positioning After Lung Transplantation

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ABSTRACT

BACKGROUND Prone positioning has become a standard therapy in acute respiratory distress syndrome to improve oxygenation and decrease mortality. However, little is known about prone positioning in lung transplant recipients. This large, singe-center analysis investigated whether prone positioning improves gas exchange after lung transplantation.

METHODS Clinical data of 583 patients were analyzed. Prone position was considered in case of impaired gas exchange Pa_{O_2}/fraction of oxygen in inhaled air (<250), signs of edema after lung transplantation, and/or evidence of reperfusion injury. Patients with hemodynamic instability or active bleeding were not proned. Impact of prone positioning (n = 165) on gas exchange, early outcome and survival were determined and compared with patients in supine positioning (n = 418).

RESULTS Patients in prone position were younger, more likely to have interstitial lung disease, and had a higher lung allocation score. Patients were proned for a median of 19 hours (interquartile range,15-26) hours). They had significantly lower Pa_{O_2}/fraction of oxygen in inhaled air (227 ± 96 vs 303 ± 127 mm Hg, $P = .004$), and lower lung compliance (24.8 ± 9.1 mL/mbar vs 29.8 ± 9.7 mL/mbar, $P < .001$) immediately after lung transplantation. Both values significantly improved after prone positioning for 24 hours (Pa_{O_2}/fraction of oxygen ratio: 331 ± 91 mm Hg; lung compliance: 31.7 ± 20.2 mL/mbar). Survival at 90 days was similar between the 2 groups (93% vs 96%, $P = .105$).

CONCLUSIONS Prone positioning led to a significant improvement in lung compliance and oxygenation after lung transplantation. Prospective studies are needed to confirm the benefit of prone positioning in lung transplantation.

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Prone positioning (PP) (chest/face down and back up) has become a standard treatment for acute respiratory distress syndrome patients to improve impaired gas exchange.[1,2] PP within 48 hours after the onset of acute respiratory distress syndrome significantly decreased early mortality compared with patients treated in the supine position.[3] The main underlying mechanisms of PP are alterations in the distribution of alveolar ventilation, redistribution of blood flow, and improved matching of local ventilation and perfusion, thus reducing regions with low ventilation/perfusion ratios.[4]

Early outcome after lung transplantation is directly related to the quality of the donor lungs as well as to the

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TABLE 1 Comparison of Donor and Recipient Demographics

Demographics	All Patients (N = 583)	Group Prone Patients (n = 165)	Group Supine Patients (n = 418)	*P* Value
Donors				
Age, y	53 (36-60)	48 (36-55)	53 (36-60)	<.001[a]
Height, cm	170 ± 10	169 ± 10	171 ± 11	.011[a]
Weight, kg	74 ± 12	70 ± 14	74 ± 18	.018[a]
Body mass index, kg/m^2	24 ± 4.8	24 ± 4.0	25 ± 4.9	.262
Blood group				.695
A	276 (47)	84 (51)	192 (46)	
B	79 (14)	21 (13)	58 (14)	
O	173 (30)	43 (26)	130 (31)	
AB	55 (9)	17 (10)	38 (9)	
Donation type				.703
Smoking				.058
Yes	155 (27)	53 (32)	102 (24)	
No	333 (57)	84 (51)	249 (60)	
Unknown	95 (16)	28 (17)	67 (16)	
Total intubation days	3 (2-6)	3 (2-6)	3 (2-5)	.569
Abnormalities in roentgenogram or CT	234 (40)	54 (33)	180 (43)	.095
Purulent secretions in BSC	103 (18)	35 (21)	68 (16)	.159
Reported aspiration	53 (9)	20 (12)	33 (8)	.274
Last Pa_{O_2}, mm Hg	430 ± 102	424 ± 104	440 ± 99	.246
Last Pa_{CO_2}, mm Hg	40 ± 6.5	40 ± 6.9	40 ± 6.3	.286
High-risk Oto score >7	38 (7)	9 (5)	29 (7)	.513
Recipients				
Age, y	49 (30-60)	49 (30-58)	53 (36-60)	.015[a]
Height, cm	168 ± 10	168 ± 12	169 ± 11	.284
Weight, kg	63 ± 16	62 ± 17	63 ± 15	.799
Body mass index, kg/m^2	22 ± 4	22 ± 4.4	22 ± 3.6	.844
Male sex	323 (55)	82 (50)	241 (58)	.080
High urgent status	77 (13)	31 (19)	46 (11)	.080
Lung allocation score	36 (33-57)	40 (34-57)	36 (33-41)	<.001[a]
Bridge				<.001[a]
Mechanical ventilation	10 (2)	6 (4)	4 (1)	
Extracorporeal life support	59 (10)	28 (17)	31 (7)	
Awake extracorporeal life support bridge	24 (4)	11 (7)	13 (3)	.836

[a]Statistically significant ($P < .05$). Data are presented as median (interquartile range), mean ± SD, or n (%). BSC, bronchoscopy; CT, computed tomography.

development of primary graft dysfunction (PGD), a form of acute lung injury characterized by pulmonary edema and impaired gas exchange.[5,6] PGD-induced refractory hypoxemia after lung transplantation and acute respiratory distress syndrome have a similar underlying pathophysiology with limited therapeutic options available.[7] An experimental animal study and in a study of 40 human organ donors with hypoxemia and atelectasis showed that PP protects the organ from further lung damage.[8,9]

PP after lung transplantation was previously described in a small Spanish case series. The authors found that PP significantly improved gas exchange in patients with refractory hypoxemia after lung transplantation.[10] However, a large-scale analysis of this topic is not found in the literature.

This retrospective study evaluated our practice of PP early after lung transplantation. We hypothesized that PP is a safe and efficient treatment option to improve gas exchange in patients with impaired primary organ function.

PATIENTS AND METHODS

STUDY DESIGN. This retrospective, single-center study included all patients who underwent lung transplantation between January 2014 and December 2019 at the Medical University of Vienna, Vienna, Austria. The study protocol was approved by the Medical University of Vienna Ethics Committee (EK #2234/2017). The need for informed consent was waived due to the retrospective nature of the study.

Patients in PP within the first 12 hours after lung transplantation were identified. PP was considered in case of impaired gas exchange with a Pa_{O_2}/fraction of oxygen in inhaled air (P/F ratio) of <250 mm Hg, signs of edema in bronchoscopy at the end of transplantation, and/or evidence of reperfusion injury in a chest roentgenogram. Patients with hemodynamic instability (considering blood pressure, cardiac output, and/or vasopressor dose) or active bleeding were not proned. Patients were placed in PP for at least 12 hours before being turned back to the supine position. The decision to turn patients back to the supine position depended on the recovery of lung function (compliance and P/F ratio).

Demographic and clinical data were retrieved from the Eurotransplant database and from the institutional transplant database and intensive care data management system archives (IntelliSpace Critical Care and Anesthesia, Philips).

Patients were put in PP by intensive care unit staff using adequate beds with special mattresses and features developed for position therapy on the intensive care unit (Citadel bed, Arjo Austria). In addition, turning required 4 nurses, and being performed in the morning was preferred.

Ventilation protocols are highly standardized in our institutions and are similar for patients in the prone and supine position. Pressure control mode is the primary postoperative ventilation mode, followed by pressure support ventilation and spontaneous positive pressure breathing before extubation. The driving pressure is set to achieve a tidal volume of 6 to 8 mL/predicted body weight according to lung protective ventilation strategy limiting the peak airway pressure to 30 cm H_2O and adjusting the driving pressure to <15 mbar if possible. The positive end-expiratory pressure is carefully adjusted to optimize lung compliance. Prolonged

TABLE 2 Perioperative Outcome of Patients Who Received a Transplant

Variable	All Patients (N = 583)	Group Prone Patients (n =165)	Group Supine Patients (n = 418)	*P* Value
Ex vivo lung perfusion	22 (4)	5 (3)	17 (4)	.206
Ischemic time, min	355 (318-419)	359 (323-419)	355 (318-416)	.439
Type of transplant				<.001[a]
Whole lungs	283 (49)	54 (33)	229 (55)	
Size reduction	241 (41)	93 (56)	148 (35)	
Lobar transplant	41 (7)	18 (11)	23 (5)	
Type of intraoperative support				
No support	2 (0.5)	2 (1)	0	.328
Intraoperative extracorporeal membrane oxygenator	573 (98)	162 (98)	411 (98)	
Cardiopulmonary bypass	8 (1)	1 (1)	7 (2)	
Surgery duration, min	285 (235-335)	285 (235-335)	285 (252-330)	.971
Intraoperative transfusions, units				
Packed red blood cells	4 (2-7)	4 (3-7)	4 (2-6)	.002[a]
Fresh frozen plasma concentrates	9 (5-14)	11 (8-14)	9 (5-12)	<.001[a]
Prolonged postoperative venoarterial extracorporeal membrane oxygenation	108 (19)	48 (30)	60 (14)	<.001[a]
Primary graft dysfunction				<.001[a]
Grade 0	507 (87)	124 (75)	383 (92)	
Grade 1	17 (3)	10 (6)	7 (2)	
Grade 2	16 (3)	8 (5)	8 (2)	
Grade 3	13 (2)	9 (5)	4 (1)	
"Ungradable"	29 (5)	14 (8)	15 (4)	
Induction	462 (79)	142 (86)	320 (77)	.011[a]
Length of mechanical ventilation, d	2 (1-9)	3 (2-9)	1 (1-2)	<.001[a]
Length of stay				
Intensive care unit, d	10 (6-29)	12 (7.-29)	6 (4-10)	<.001[a]
Hospital, d	25 (19-55)	35 (21-55)	25(19-35)	<.001[a]
Survival at 90 days	557 (96)	154 (93)	403 (96)	.105

[a]Statistically significant ($P < .05$). Data are presented as n (%) or median (interquartile range).

mechanical ventilation is defined as mechanical ventilation for >72 hours after lung transplantation. Weaning protocols are not standardized, because we aim to meet the individual needs. Respiratory settings, oxygenation, and gas exchange variables are checked and reevaluated regularly.

Ventilatory setting and blood gases were recorded before, during, and after PP. Dynamic lung compliance was calculated by tidal volume/peak pressure – positive end-expiratory pressure for the purpose of this study.

STATISTICAL ANALYSIS. Statistical analysis was performed using GraphPad Prism 8.0 (GraphPad Software) and R 4.1.1 (R Core Team; 2021). For survival analysis and Kaplan-Meier curves, IBM SPSS Statistics 26.0 software (IBM Corp) was used. Continuous data are presented as mean ± SD when normally distributed or as the median with interquartile range (IQR) when nonnormally distributed. Categorical data are summarized using absolute and relative frequencies. To compare donor characteristics (Table 1) as well as patient characteristics (Table 2) between the supine and the PP group, *t* tests or 1-way analysis of variance were performed for metric variables and χ^2 tests or the Fisher test for categorical variables. *P* values have to be interpreted in a descriptive way and were not corrected for multiple testing.

RESULTS

DONOR CHARACTERISTICS. Details of donors are summarized in Table 1. Most grafts came from donation after brain death donors (95%), with cerebrovascular events being the most common cause of death. A smoking history was reported in 27% of donors. Abnormalities (infiltrations, pneumothoraces, and contusions) were found in 40% of donor roentgenograms or computed tomographic scans. Of note, none of these abnormalities were different between the PP and the supine group. However, donors in the PP group were slightly younger, with a median age of 48 years (IQR 36-55 years) compared with 53 years (IQR 36-60 years) in the control group ($P < .001$).

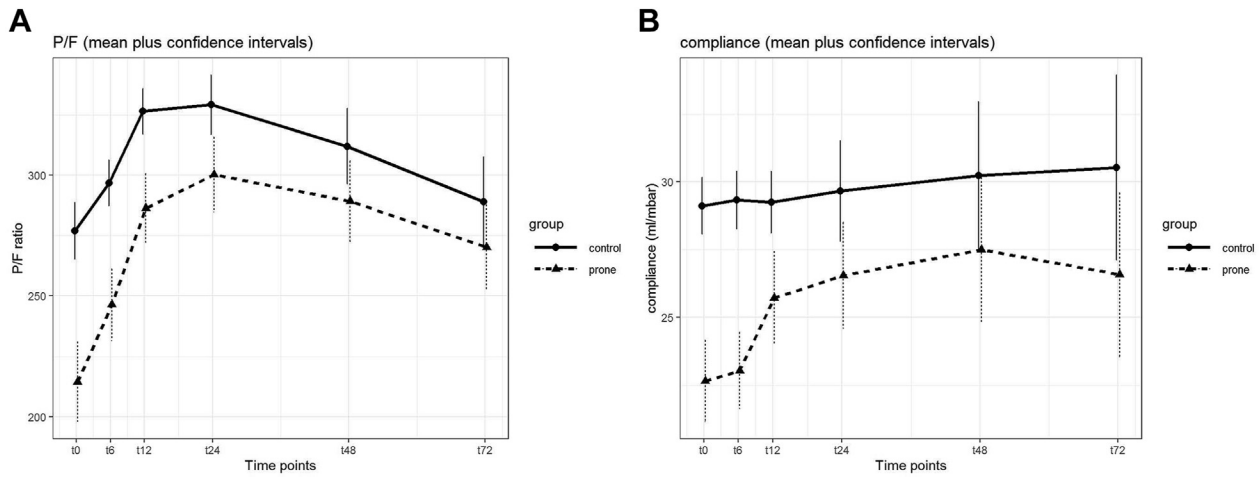


FIGURE 1 (A) Pao_2/fraction of oxygen in inhaled air (P/F) ratio and (B) lung compliance of the 2 study groups upon arrival at the intensive care unit (t0 hours) and during the first 72 hours after transplant. Compared with controls (n = 418), the group of proned patients (n = 165) had significantly worse indicators immediately after transplantation but improved significantly during prone positioning.

RECIPIENT DEMOGRAPHICS AND PROCEDURAL ASPECTS. Most patients in the PP group had interstitial lung disease, whereas chronic obstructive pulmonary disease (COPD)/α_1-antitrypsin deficiency (A1AT) was the most relevant indication for lung transplantation in the supine group. Patients in the PP group had a higher lung allocation score and were bridged more often by extracorporeal membrane oxygenator (17% vs 7%) or mechanical ventilation (4% vs 1%, $P < .001$). Of note, 24 of 59 of extracorporeal membrane oxygenator-bridged recipients were bridged awake.

The transplant procedure differed significantly between the groups. Downsizing had to be performed more often in the PP group, resulting in 56% nonanatomical resection of parts of the middle lobe or lingula and 11% bilobar/trilobar transplantations. Size reduction was less often necessary in the supine group, with only 35% nonanatomical resections and 5% bilobar/trilobar transplantations ($P < .001$).

Surgical time and number of intraoperative packed red blood cells were comparable in both groups. However, platelet concentrates were more often administered in the PP group, most likely based on the higher proportion of patients bridged with extracorporeal life support (Table 2).

IMPACT OF PP ON GAS EXCHANGE. Patients in PP group had significantly lower P/F ratios (227 ± 96 mm Hg vs 303 ± 127 mm Hg, $P = .004$) and a lower dynamic lung compliance (24.8 ± 9.1 mL/mbar vs 29.8 ± 9.7 mL/mbar, $P < .001$) at the end of the operation compared with patients in supine group. Consequently, PP patients had higher rates of PGD ($P < .001$). PP was started in all patients immediately upon intensive care unit arrival and was maintained for a median of 19 hours (IQR, 15-26 hours). Of note, the P/F ratio and dynamic lung compliance significantly improved during PP (Figure 1, Supplemental Figure 1, Table 3, Supplemental Table 1).

PP IN PATIENTS ON POSTOPERATIVE PROLONGED EXTRACORPOREAL MEMBRANE OXYGENATOR SUPPORT. In our institution, postoperative prolongation of venoarterial extracorporeal membrane oxygenation does not exclude a patient from PP. In fact, 48 of 108 patients on postoperative extracorporeal membrane oxygenator support were placed in PP upon arrival at the intensive care unit.

Also, in this subgroup, the P/F ratio (148 mm Hg [IQR, 81.3-219.3 mm Hg] to 317 mm Hg,[IQR, 153.9-403.3 mmHg]; $P = .0002$) and dynamic lung compliance (16.6 mL/mbar [IQR, 12.2-26.4 mL/mbar] to 21.8 mL/mbar [14.6-29.8 mL/mbar]; $P = .05$) improved significantly during PP. The median extracorporeal membrane oxygenator time was 3 days (IQR, 2-5.5 days).

Serious adverse events related to PP (such as kinking of extracorporeal membrane oxygenator lines, dislocation of extracorporeal membrane oxygenator cannulas, etc) were noted. A specific finding that frequently occurred after PP was facial swelling. However, once patients were back in the supine position, the swelling usually resolved within 2 hours.

FACTORS ASSOCIATED WITH A RESPONSE TO PP. A further set of analyses was performed to identify factors that could predict the response to PP. For this purpose, changes in P/F ratio and dynamic lung compliance between intensive care unit admission and measurements 6 hours after intensive care unit admission) were

defined as outcome variable. In an exploratory analysis, only the duration of surgery, $Paco_2$, and arterial pH value at the end of surgery were associated with the response to PP (Supplemental Figure 2; Supplemental Table 2). Grouping patients into different diagnosis (interstitial lung disease, COPD/A1AT, cystic fibrosis) revealed a similar effect of PP in all groups (Figure 2).

SHORT- AND LONG-TERM OUTCOME. Length of mechanical ventilation was significantly longer in the PP group (median 3 days [IQR, 3-7 days] vs 1 day [IQR, 1-2 days]; $P < .001$), and tracheostomy was more likely in patients in the PP group (25%) compared with the supine group (16%; $P = .005$). This also translated to longer intensive care unit stays and longer hospital stays. Despite this, 90-day survival was similar between the 2 groups (93% vs 96%, $P = .105$). Long-term survival was also comparable between the groups. Overall survival did not differ in either study group ($P = .882$). The 5-year survival was 75.4% in the prone group and 78% in the supine group (Figure 3).

TABLE 3 Detailed Analysis of Factors to Find Response to Prone Positioning

Variable	Group Prone Patients Mean ± SD	Group Supine Patients Mean ± SD	*P* Value
End of operation			
Pao_2, mm Hg	121 ± 48	137 ± 54	.004[a]
$Paco_2$, mm Hg	50.7 ± 11.9	45.6 ± 10.5	<.001[a]
pH, mol/L	7.38 ± 0.09	7.40 ± 0.09	.020[a]
Lactate, mmol/L	2.2 ± 1.0	2.3 ± 1.4	.784
Fio_2,% oxygen/100	0.6 ± 0.2	0.5 ± 0.1	<.001[a]
PEEP, cm H_2O	8.1 ± 1.8	7.2 ± 1.3	<.001[a]
Peak, cm H_2O	25.2 ± 3.9	22.7 ± 3.3	<.001[a]
Tidal volume, mL	409 ± 129	443 ± 117	.018[a]
Compliance, mL/mbar	24.8 ± 9.1	29.8 ± 9.7	<.001[a]
P/F ratio, mm Hg	227 ± 96	303 ± 127	<.001[a]
24 hours			
Pao_2, mm Hg	116 ± 24	118 ± 32	.562
$Paco_2$, mm Hg	45.0 ± 8.6	46.3 ± 8.9	.244
pH, mol/L	7.44 ± 0.07	7.42 ± 0.07	.067
Lactate, mmol/L	2.0 ± .9	1.8 ± .9	.068
Fio_2,% oxygen/100	0.4 ± 0.1	0.4 ± 0.1	.254
PEEP, cm H_2O	7.8 ± 1.5	7.1 ± 1.3	<.001[a]
Peak, cm H_2O	23.2 ± 4.8	21.1 ± 4.6	<.001[a]
Tidal volume, mL	438 ± 143	420 ± 123	.257
Compliance, mL/mbar	31.7 ± 20.2	37.1 ± 30.9	.110
P/F ratio, mm Hg	331 ± 91	354 ± 110	.071
48 hours			
Pao_2, mm Hg	109 ± 26	111 ± 31	.695
$Paco_2$, mm Hg	50.1 ± 10.6	48.2 ± 8.6	.178
pH, mol/L	7.41 ± 0.07	7.42 ± 0.07	.523
Lactate, mmol/L	1.3 ± 0.5	1.3 ± 0.6	.560
Fio_2,% oxygen/100	0.4 ± 0.1	0.4 ± 0.1	.356
PEEP, cm H_2O	7.6 ± 1.4	6.9 ± 1.6	.005[a]
Peak, cm H_2O	21.1 ± 5.7	19.7 ± 5.9	.132
Tidal volume, mL	421 ± 149	403 ± 166	.490
Compliance, mL/mbar	42.1 ± 42.8	41.8 ± 41.8	.960
P/F ratio, mm Hg	308 ± 94	326 ± 104	.277
72 hours			
Pao_2, mm Hg	115 ± 39	110 ± 38	.475
$Paco_2$, mm Hg	52.2 ± 11.84	49.5 ± 9.9	.166
pH, mol/L	7.41 ± 0.06	7.42 ± 0.06	.359
Lactate, mmol/L	1.1 ± 0.45	1.2 ± 0.5	.658
Fio_2,% oxygen/100	0.4 ± 0.11	0.4 ± 0.1	.470
PEEP, cm H_2O	7.8 ± 1.7	7.1 ± 1.8	.040[a]
Peak, cm H_2O	21.1 ± 6.8	20.0 ± 5.8	.392
Tidal volume, mL	413 ± 166	379 ± 143	.271
Compliance, mL/mbar	42.1 ± 39.7	41.5 ± 51.1	.943
P/F ratio, mm Hg	291 ± 76	305 ± 133	.528

[a]Statistically significant ($P < .05$). Changes of P/F ratio and dynamic lung compliance between arrival in the intensive care unit and measurements performed 72 hours after intensive care unit admission were defined as outcome variables. Fio_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; P/F, Pao_2/fraction of oxygen in inhaled air.

COMMENT

This retrospective study investigated the effect of PP in a large cohort of lung transplant recipients. We could demonstrate that PP resulted in a profound improvement of oxygenation and lung compliance in patients with impaired gas exchange at the end of the operation. In addition, we could show that PP is feasible even in patients who require postoperative extracorporeal membrane oxygenator support.

PGD after lung transplantation remains a major challenge in the perioperative course, associated with significant morbidity and mortality.[11] Treatment options of PGD are similar to those of acute respiratory distress syndrome, including protective mechanical ventilation, fluid restriction, and less established therapies such as inhaled nitric oxide, aerosolized prostacyclin (epoprostenol), and C1 esterase inhibitors.[12-18]

Since its initial description by Piehl and Brown[2] in 1976, PP has been increasingly used to treat acute respiratory distress syndrome.[1] Moreover, during the current coronavirus disease 2019 pandemic, PP has become a standard treatment strategy for patients with coronavirus disease 2019-associated acute respiratory distress syndrome, resulting in favorable outcomes even in nonintubated patients with hypoxemic respiratory failure.[19,20]

Effects of PP for refractory hypoxemia after lung transplantation were previously described in 22 patients. PP resulted in a significantly increased P/F ratio, and despite the impaired early organ function, 1-year mortality was comparable to a cohort of control lung transplantation recipients.[10] Our study could confirm this initial experience with a steep increase of the P/F ratio in patients in PP. Improved P/F ratios were also found in the supine position group, but the obvious selection bias of functionally worse grafts in the PP group makes a direct comparison difficult. In our opinion, the effect of PP can best be seen in the improvement of ventilation mechanics. Lung compliance improved

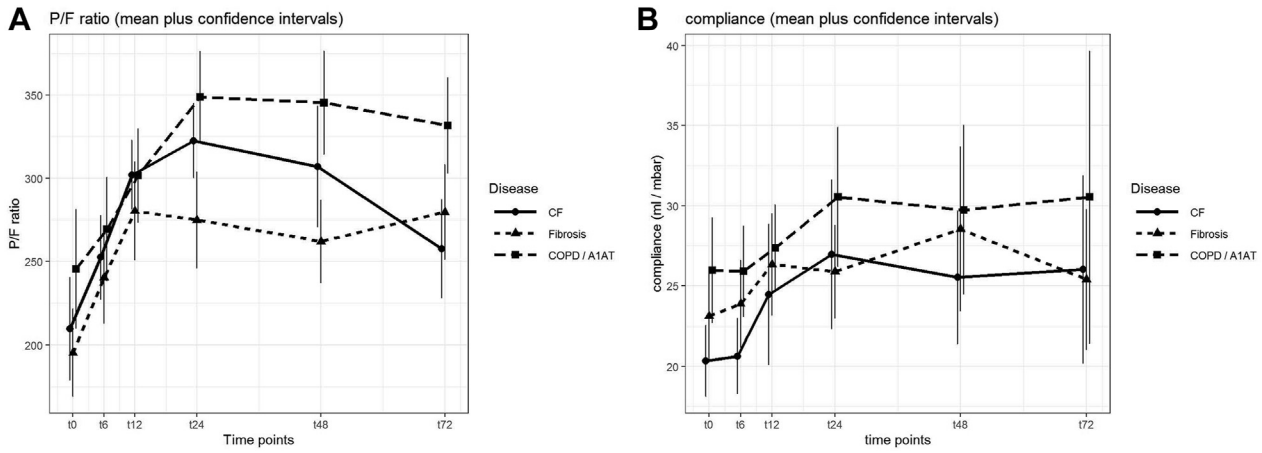
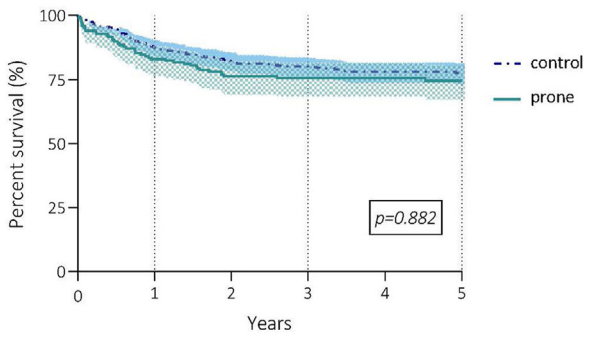


FIGURE 2 Improvement in the (A) Pao_2/fraction of oxygen in inhaled air (P/F) ratio and (B) lung compliance was not restricted to a specific recipient diagnosis. (A1AT, α_1-antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease.)

significantly in patients in PP and remained unchanged after repositioning to the supine position.

Because ventilatory mechanics after transplantation are closely related to the recipient's underlying disease (restrictive or obstructive), we performed an additional set of analyses and divided patients into interstitial lung disease, COPD/A1AT, and cystic fibrosis. Interestingly, all 3 groups showed similar improvement in lung compliance as well as P/F ratio during PP. Moreover, in an exploratory analysis, only surgery time, $Paco_2$, and arterial pH at the end of transplantation could predict the response to PP.



subjects at risk	0	1	2	3	4	5
control	418	366	341	278	220	157
prone	165	137	124	97	1419	71

FIGURE 3 Overall survival did not differ between the study groups (log-rank $P = .882$). The shaded areas indicate the 95% CI.

In our lung transplantation center, the decision for prolonged extracorporeal membrane oxygenator support is made on functional assessments of the graft after decannulation. In our study, 48 patients of the PP group were supported by prolonged postoperative extracorporeal membrane oxygenator support. None of these patients experienced extracorporeal membrane oxygenator-related complications.

This study has several limitations. First, this analysis is a retrospective study of a single center and might not reflect the practice of other transplant programs.

Second, selection criteria for PP of patients were based on nonvalidated clinical criteria. Therefore, it is uncertain whether patients could have similarly recovered from impaired gas exchange if they had been positioned supine.

Finally, we are currently formulating a protocol for a multicenter prospective randomized trial and hope that such a study will help to address the shortcomings of this study and further promote the role of PP in lung transplantation.

In conclusion, we could demonstrate in this study that oxygenation and pulmonary compliance significantly improved during PP in patients with impaired primary organ function. In addition, PP is feasible and safe in lung transplantation recipients who require prolonged extracorporeal membrane oxygenator support.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

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