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Original Article

Early Prone Positioning As a Rescue Therapy for Moderate-to-severe Primary Graft Dysfunction After Bilateral Lung Transplant

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Objectives: Primary graft dysfunction (PGD) affects survival after lung transplant (LT). The current hypothesis was that prone positioning (PP), proposed as a rescue maneuver to treat refractory hypoxemia due to PGD, may improve LT outcomes, especially when applied early.

Design: Bilateral LT recipients developing moderate-to-severe PGD within 24 hours from intensive care unit admission were enrolled. From January 2020 to November 2021, patients developing PGD after LT were turned prone between 24 and 48 hours after diagnosis, only in case of radiological or oxygenation worsening ("late PP" group). After November 2021, patients were routinely turned prone within 24 hours from PGD diagnosis ("early PP"). A propensity score–weighted analysis, adjusted for clinically relevant covariates, was applied.

Setting: Intensive care unit.

Participants: Bilateral LT recipients.

Interventions: Early PP, late PP, or supine position.

Measurements and Main Results: 130 LT patients were screened and 67 were enrolled. A total of 25 (37%) recipients were treated in the supine position, 24 (36%) in early PP, and 18 (27%) in late PP. After propensity score weighting, both supine treatment (estimated effect for 1 ventilator-free day = 8.23, standard error: 2.97, $p = 0.007$) and early PP treatment (estimated effect = 9.42, standard error: 2.59, $p < 0.001$) were associated with greater 28-day ventilator-free days than late PP treatment (reference). Compared with late PP, early PP was also associated with better oxygenation, driving pressure, and static respiratory system compliance. Compared with supine recipients, the early PP group showed better oxygenation at 72 hours after PGD diagnosis.

Clinical Trial Registry Number: NCT06159933

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Conclusions: Early PP in LT recipients with moderate-to-severe PGD seems to be associated with better 28-day ventilator-free days, oxygenation, and driving pressure than late PP.

Key words: primary graft dysfunction; lung transplant; prone positioning; acute respiratory distress syndrome; invasive mechanical ventilation; extracorporeal membrane oxygenation

LUNG TRANSPLANT (LT) is a life-saving treatment that can be considered for end-stage pulmonary diseases. However, despite significant improvements in the last decade, survival after LT remains lower than after other solid organ transplants.[1]

One of the most challenging problems affecting survival after LT is primary graft dysfunction (PGD), a form of acute lung injury occurring up to 72 hours after surgery that is caused by severe pulmonary damage induced by ischemia and/or reperfusion, with consequent pulmonary edema, uncontrolled inflammation, and impaired gas exchange.[2] Clinically, PGD is characterized by diffuse bilateral infiltrates on chest x-ray and refractory hypoxemia with an arterial-partial-pressure-of-oxygen (PaO_2)-to-fractional-inspired-oxygen (FiO_2) ratio that could reach values below 300 mmHg in the moderate form known as PGD2, and below 200 mmHg in the most severe form, defined as PGD3. PGD3 has been reported to occur in almost 30% of LTs, is associated with longer hospital length of stay, and carries a risk of mortality beyond 90 days.[3,4] Therapies available in the case of moderate-to-severe PGD are mainly supportive.[5] According to recent findings, promising results have been obtained with prone positioning (PP), a rescue maneuver that has shown great benefits in patients with acute respiratory distress syndrome (ARDS).[6,7] Two recent retrospective studies, enrolling 187 LT recipients showed that PP significantly improved gas exchange and limited the adverse effects related to persistent refractory hypoxemia without impacting the survival rate.[8,9] Moreover, Hoetzenecker et al., enrolling 116 LT patients treated with no extracorporeal membrane oxygenation (ECMO), 343 with intraoperative ECMO, and 123 with intraoperative and prolonged postoperative ECMO showed that intraoperative ECMO results in superior survival compared with LTs without extracorporeal support. Moreover, the use of prophylactic postoperative ECMO prolongation was associated with excellent outcomes in recipients with pulmonary hypertension and patients with questionable graft function at the end of implantation.[10] However, standardized criteria to use PP in the case of moderate-to-severe PGD, more than according to a PaO_2/FiO_2 ratio <250 mmHg[8] or regardless of the degree of PGD,[9] are still matters of debate, and no data are available about the best timing for turning these patients prone.

Therefore, the present study was designed to verify the hypothesis that patients developing moderate-to-severe PGD within the first 24 hours after intensive care unit (ICU) admission could benefit from PP, especially when applied earlier (within 24 hours from diagnosis) rather than later (24-48 after diagnosis). Specifically, the primary outcome was 28-day ventilator-free days, and secondarily, the impact of early PP on short-term outcomes, gas exchanges, and respiratory mechanics were evaluated.

Materials and Methods

The study was approved by the local Institutional Ethics Committee (reference 4539/AO/18) and conducted following the principles of Good Clinical Practice outlined in the Declaration of Helsinki (Clinical Trial Registry Number: NCT06159933). Informed consent was obtained from all participants. This article was written following the STROBE checklist (Supplementary Table 1). All patients undergoing first bilateral LT at Padua University Hospital were retrospectively screened between January 2020 and December 2021 and prospectively enrolled between January 2022 and April 2023. Only LT recipients developing PGD grade 2 (defined by the presence of bilateral radiographic infiltrates and a PaO_2/FiO_2 ratio of <300 mmHg) or 3 (defined by the presence of bilateral radiographic infiltrates and a PaO_2/FiO_2 ratio of <200 mmHg) within 24 hours from ICU admission were enrolled.[5] Predefined exclusion criteria were: (1) age <18 years old; (2) single transplant; (3) retransplant; (4) invasive mechanical ventilation (IMV), venous-venous (V-V) or venous-arterial (V-A) ECMO before surgery; (5) PGD <2; (6) contraindications to PP[11,12]; and (7) refusal of consent.

The study design is depicted in Figure 1. According to the local protocol, until November 2021, all patients developing PGD >1 after LT were monitored in the supine position for at least 24 hours, aiming to optimize mechanical ventilation settings and right ventricular function before considering PP. Only in the case of radiological worsening or reduction in PaO_2/FiO_2 ratio were patients turned prone, generally between 24 and 48 hours after diagnosis (late PP group); otherwise, they were maintained supine (supine group). Conversely, starting from November 2021, the local protocol was updated, and all LT recipients developing PGD >1 underwent a mandatory stabilization period of 12 to 24 hours and only at the end of this period were routinely turned prone within 24 hours after the diagnosis of PGD (early PP).[6] Patients were placed in PP for at least 16 hours before being turned back to the supine position when meeting predefined criteria previously published by Guèrin et al.[6] Demographic and clinical data were retrieved from electronic health records and included baseline patient characteristics, underlying end-stage lung diseases, intraoperative characteristics, and data collected after ICU admission.

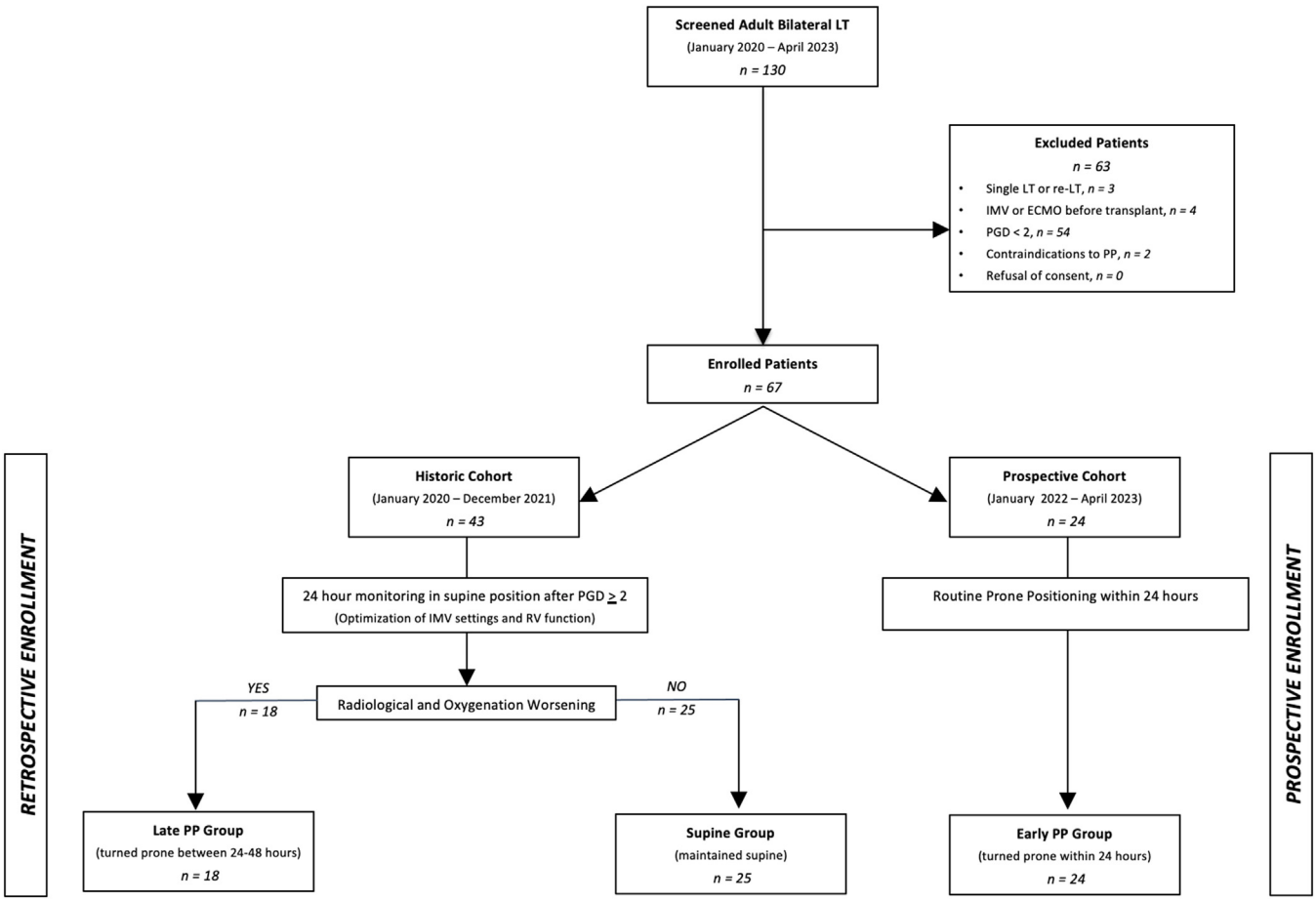

Fig 1. Flowchart. ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; LT, lung transplant; PGD, primary graft dysfunction; PP, prone position; RV, right ventricle.

All transplants were performed with central V-A ECMO support, minimizing exposure time to avoid inflammation.[10,13,14] At the end of the surgery, four 28-Ch-diameter chest tubes were positioned, one basal curved and one apical straight for each side. Anesthetic management for LT has been protocolized in the authors' institution since 2021, consistent with international recommendations,[15] as mentioned in previous publications.[16-18] Immunosuppressive treatments and ventilation protocols were highly standardized and equal among patients in prone and supine positions.[16-18] Volume control mode was the primary postoperative ventilation mode, followed by pressure support ventilation. The ventilatory strategy aimed to achieve a tidal volume of 6 mL/donor's predicted body weight (or lower) and a driving pressure (DP) below 14 cmH_2O.[19,20] The positive end-expiratory pressure was carefully adjusted to minimize overdistension and/or atelectasis according to electrical impedance tomography, as previously published[21]; weaning protocols were standardized, as described by Boscolo et al.[13] Respiratory settings, oxygenation, and gas exchange variables were checked and re-evaluated regularly during and after PP. For all patients, baseline arterial blood gas (ABG) was defined as the worst ABG collected within the first 24 hours after ICU admission (and before PP). In the case of multiple prone positions, only parameters derived from the first prone cycle were recorded. Static respiratory compliance (Crs) was calculated by tidal volume/(plateau pressure − end-expiratory pressure) and DP by plateau pressure − end-expiratory pressure.[22] The 28-day ventilator-free days were defined as the number of days of unassisted breathing to day 28 without having to reinstitute invasive ventilation. Patients who died before day 28 were assigned 0.[23]

Statistical Analysis

Continuous data are presented as means and standard deviations (SDs) when normally distributed or as medians with interquartile ranges (IQRs) when non-normally distributed. Categorical data are summarized using absolute and relative frequencies. This study is a pilot investigation, and the sample size was not calculated. There were no missing data. To compare patient characteristics, Student's *t*-test and ordinary one-way analysis of variance (or Mann-Whitney U and Kruskal-Wallis tests in the case of non-normality) were performed for metric variables, and the Chi-squared or Fisher's exact test were used for categorical variables. In the case of multiple

comparisons, a post-hoc analysis using the Benjamini method was applied. Spearman's coefficient was used for correlations between ABGs collected at the end of PP and 12 hours after resupination.

To account for potential confounding related to the nonrandom allocation of patients to the three groups (early PP, late PP, and supine), a propensity-score method was employed. According to clinical judgment, age, lung allocation score (LAS), body mass index (BMI), and a predefined continuous time variable, calculated as the time since the start of accrual for the study population and patient's enrollment, were considered as covariates.

Propensity scores for the three treatment groups were calculated using gradient-boosted logistic regression.[24] A tree-based regression model built in an iterative fashion was used to estimate the weights.[25] The average treatment effect on the population was used as an estimate. The mean of the absolute standardized mean difference (ASMD) was used as a measure of balance. Supplementary Table 2 describes the maximum of the ASMD and the minimum of the p-value across all pairwise comparisons for each pretreatment covariate. Information about the effective sample sizes for each treatment group is reported in Supplementary Table 3. A graphical representation of the comparisons before and after weighting of the ASMD between the treatment groups on the pretreatment covariates is reported in Supplementary Figure 1. Supplementary Figure 2 depicts the pairwise minimum p-values for differences between the individual treatment groups and observations in all other treatment groups.

A propensity score–adjusted regression was performed and provided the estimated effect, standard error (SE), and p-value. Analyses were performed using R software version 3.5.2 with the "twang" package and GraphPad Prism 8.0 (GraphPad Software). All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

A total of 130 consecutive bilateral LT patients were screened, and 67 recipients meeting inclusion criteria were enrolled in the study (Fig 1). Of those enrolled, 25 (37%) patients were treated in the supine position (supine group) while 42 (63%) were turned prone, of whom 24 (36%) were turned within 24 hours from diagnosis of PGD (early PP group) and 18 (27%) between 24 and 48 hours after diagnosis (late PP group). Patients' characteristics before and after bilateral LT are listed in Table 1. No differences concerning demographic characteristics, comorbidities, underlying end-stage lung diseases, or intraoperative parameters were recorded between the three subgroups (Table 1).

Among patients treated with PP, the overall median number of pronation cycles was 1 (IQR: 1-2), while the overall median cycle duration was 16 (IQR: 12-18) hours (Table 2).

Short-term Outcomes

As shown in Table 1, the 28-day ventilator-free days were significantly different among the three subgroups (25 [IQR: 21-26] days in the supine group *v* 26 [IQR: 19-26] days in the early PP group *v* 12 [IQR: 2-20] days in the late PP group, $p = 0.002$). Specifically, the main difference was found by analyzing the overall length of IMV ($p < 0.001$) rather than the duration of non-IMV ($p = 0.141$) in different subgroups, as reported in Table 1.

The propensity score–weighting analysis confirmed these findings. Effective sample size, after propensity score weighting, in the early, late, and supine groups were 24, 16, and 24 patients, respectively. Both supine treatment (estimated effect per 1 ventilator-free day = 8.23, SE: 2.97, $p = 0.007$) and early PP treatment (estimated effect per 1 ventilator-free day = 9.42, SE: 2.59, $p < 0.001$) were associated with greater 28-day ventilator-free days than the late PP treatment (reference) (Table 1).

As shown in Supplementary Table 2, for all pretreatment variables, the maximum ASMD, despite remaining high, decreased, and the minimum p-values increased after applying the weights arising from the stopping method. This is confirmed graphically in Supplementary Figures 1 and 2.

Also, significant differences between groups were recorded in PGD grade at 72 hours after LT ($p < 0.001$). The need for re-tracheal intubation and/or tracheostomy, the rate of rejection at 30 days after LT, hospital length of stay, and in-hospital mortality were not different among subgroups (Table 1). Among patients undergoing PP, either early or late, 11 patients (6 early PP and 5 late PP) experienced at least one complication due to PP, with no significant difference between the two groups (Table 1); in particular, pressure ulcers (10 of 11 patients) and wound dehiscence requiring surgical revision (3 of 11 patients) were the most common complications. In contrast, no life-threatening adverse events (ie, endotracheal tube removal, dislodgement of vascular catheter or surgical drainages, or malignant arrhythmias) occurred.

Gas Exchanges and Respiratory Mechanics

Considering baseline gas exchanges and respiratory mechanics, no differences were found between groups within the first 24 hours after ICU admission (Table 2).

Focusing on prone patients, at the end of pronation, PaO_2/FiO_2 was significantly higher in the early PP group (330 ± 65 mmHg) compared with the late PP group (250 ± 62 mmHg, $p < 0.001$), while no differences were found considering $PaCO_2$, pH, DP, or Crs (Table 2). Moreover, the early PP group maintained higher PaO_2/FiO_2 values, and lower DP and Crs compared with the late PP group at 12 hours after resupination (respectively, 332 ± 70 mmHg *v* 230 ± 53 mmHg, $p < 0.001$; 8 ± 6 *v* 14 ± 1 cmH_2O, $p = 0.041$; 48 ± 9 *v* 37 ± 4 mL/cmH_2O, $p = 0.017$). Similar findings were recorded considering the mean changes (Δ) from baseline values of ABG parameters, with significantly greater $\Delta PaO_2/FiO_2$ ratio in the early PP group than

Table 1
Baseline Characteristics of Lung Transplant Recipients

	Early PP, N = 24 (36)	Late PP, N = 18 (27)	Supine Position, N = 25 (37)	Overall p-Value	Early PP *v* Late PP	Early PP *v* Supine	Late PP *v* Supine
Baseline characteristics							
Age, y	55 [42-61]	52 [36-59]	61 [45-64]	0.168	0.350	0.350	0.190
Male sex, n (%)	16 (67)	10 (56)	20 (80)	0.213	0.534	0.343	0.104
BMI, kg/m^2	26 [22-28]	25 [24-27]	26 [24-28]	0.801	0.945	0.934	0.934
Corticosteroids, n (%)	7 (29)	8 (44)	10 (40)	0.566	0.346	0.551	0.999
O_2 therapy, n (%)	20 (83)	17 (94)	25 (100)	0.046	0.371	0.050	0.418
Diabetes, n (%)	3 (13)	4 (22)	3 (12)	0.833	0.437	1.000	0.427
Pulmonary arterial hypertension, n (%)	17 (70)	11 (61)	17 (68)	0.654	0.530	1.000	0.750
Underlying diseases							
Septic*, n (%)	3 (13)	4 (22)	3 (12)	0.548	0.437	0.667	0.217
Interstitial†, n (%)	17 (70)	10 (56)	15 (60)	0.566	0.346	0.551	0.999
Obstructive‡, n (%)	4 (17)	4 (22)	7 (28)	0.663	0.706	0.496	0.736
LAS	37 [34-47]	37 [34-47]	39 [33-44]	0.059	0.060	0.999	0.060
OTO score	3 [3-6]	4 [4-5]	5 [3-7]	0.712	0.924	0.769	0.769
Intraoperative characteristics							
Organ Care System, n (%)	4 (17)	2 (11)	4 (16)	0.867	0.685	0.999	0.999
Time of LT, min	350 [288-450]	375 [325-473]	380 [341-418]	0.927	0.986	0.986	0.986
Blood transfusion, units	2 [1-5]	4 [2-6]	3 [1-5]	0.181	0.223	0.736	0.223
Intraoperative ECMO, n (%)	24 (100)	16 (100)	25 (100)	0.999	0.177	1.000	0.999
After LT							
PGD at baseline	2 [2-3]	3 [2-3]	2 [2-3]	0.161	0.173	0.843	0.173
Grade 2	11 (46)	8 (44)	15 (60)	0.600	0.756	0.776	0.365
Grade 3	13 (54)	10 (56)	10 (40)				
PGD at 72 h	1 [0-2]	3 [2-3]	2 [2-2]	<0.001	<0.001	0.006	0.011
Grade 1 or 0	15 (63)	0 (0)	6 (24)	<0.001	<0.001	0.010	0.032
Grade 2 or 3	9 (37)	18 (100)	19 (76)				
Renal replacement therapy, n (%)	1 (4)	3 (16)	3 (12)	0.415	0.297	0.297	0.682
Invasive mechanical ventilation, d	3 [2-7]	13 [6-24]	2 [1-5]	<0.001	0.001	0.716	<0.001
Noninvasive mechanical ventilation, d	0 [0-2]	2 [0-3]	0 [0-2]	0.141	0.050	0.557	0.142
Re-tracheal intubation and/or tracheostomy, n (%)	5 (21)	5 (28)	6 (24)	0.872	0.523	1.000	1.000
Complications related to PP, n (%)	6 (33)	5 (28)	-	-	1.000	-	-
Rejection at 30 POD§, n (%)	4 (17)	3 (16)	7 (28)	0.598	1.000	0.496	0.479
H LOS, d	39 [29-45]	41 [31-54]	34 [29-43]	0.367	0.504	0.504	0.504
H mortality, n (%)	1 (4)	2 (11)	3 (12)	0.649	0.567	0.609	0.999
Time of death (after ICU admission), d	180 [180-180]	76 [42-110]	90 [55-122]	0.433	-	-	0.800
Unadjusted primary outcome							
Ventilator-free days (range: 28 d)	26 [19-26]	12 [2-20]	25 [21-26]	0.002	0.001	0.966	<0.001
Adjusted primary outcome‖	Estimated effect (per 1 ventilator-free day)	Standard error	p-Value				
Early PP *v* late PP	9.42	2.59	<0.001				
Early PP *v* supine	1.19	2.66	0.656				
Supine *v* late PP	8.23	2.97	0.007				

Data are expressed as number (percentage) or median [interquartile range].
Abbreviations: BMI, body mass index; CI, confidential interval; ECMO, extracorporeal membrane oxygenation; H, hospital; HR, hazard ratio; IBW, ideal body weight; LAS, lung allocation score; LOS, length of stay; LT, lung transplantation; PGD, primary graft dysfunction; POD, postoperative day; PP, prone positioning.
* Septic: cystic fibrosis, bronchiectasis.
† Interstitial: idiopathic pulmonary fibrosis, allergic extrinsic alveolitis, nonspecific interstitial pneumonia, fibrosing emphysema, lymphocytic interstitial pneumonia, respiratory bronchiolitis interstitial lung.
‡ Obstructive: chronic obstructive pulmonary disease, emphysema (while idiopathic pulmonary hypertension, veno-occlusive disease, connective tissue disease, α1-antitripsin deficiency, lymphangioleiomyomatosis, histiocytosis, sarcoidosis, graft-versus-host disease were absent),
§ Rejection is defined according to the International Society for Heart and Lung Transplantation criteria (ie, A3-A4 and/or B2 grade at biopsy).
‖ Primary outcome balanced according to the propensity score–weighting procedure for the variables used in the propensity score estimation (ie, age, BMI, LAS, and a predefined continuous time-dependent variable; for additional details see Supplementary Materials).

in the late PP group, but no differences between groups in $\Delta PaCO_2$, both at the end of PP or 12 hours after resupination, as summarized in Table 3 and Figure 2.

At 72 hours after PGD diagnosis, both PaO_2/FiO_2 and $\Delta PaO_2/FiO_2$ were significantly higher in the early PP group (309 ± 72 mmHg and 105 ± 79 mmHg, respectively),

Table 2
Arterial Blood Gases, Driving Pressure, and Static Respiratory Compliance at Different Time Points

	Early PP, N = 24 (36)	Late PP, N = 18 (27)	Supine Position, N = 25 (37)	Overall p-Value	Early PP *v* Late PP	Early PP *v* Supine	Late PP *v* Supine
Baseline							
PaO_2/FiO_2	215 (57)*	182 (61)*	224 (54)	0.057	0.117	0.537	0.057
(Before PP)	225 (57)*	196 (45)*	-	-	0.167	-	-
PCO_2, mmHg	45 (7)*	43 (8)*	42 (6)	0.212	0.290	0.290	0.999
(Before PP)	47 (5)*	45 (7)*	-	-	0.989	-	-
pH	7.36 (0.07)*	7.36 (0.06)*	7.38 (0.06)	0.326	0.949	0.445	0.445
(Before PP)	7.37 (0.08)*	7.40 (0.06)*	-	-	0.678	-	-
Driving pressure, cmH_2O	12 (2)	11 (1)	11 (2)	0.594	0.703	0.937	0.703
Crs, mL/cmH_2O	34 (10)	36 (6)	36 (9)	0.672	0.741	0.741	0.741
At end of prone positioning							
PaO_2/FiO_2	330 (65)	250 (62)	-	<0.001	-	-	-
PCO_2, mmHg	43 (6)	48 (6)	-	0.050	-	-	-
pH	7.34 (0.21)	7.35 (0.19)	-	0.480	-	-	-
Driving pressure, cmH_2O	11 (1)	12 (3)	-	0.733	-	-	-
Crs, mL/cmH_2O	39 (13)	33 (6)	-	0.435	-	-	-
12 h after resupination							
PaO_2/FiO_2	332 (70)	230 (53)	-	<0.001	-	-	-
PCO_2, mmHg	42 (6)	45 (6)	-	0.092	-	-	-
pH	7.37 (0.38)	7.32 (0.29)	-	0.078	-	-	-
Driving pressure, cmH_2O	8 (6)	14 (1)	-	0.041	-	-	-
Crs, mL/cmH_2O	48 (9)	37 (4)	-	0.017	-	-	-
72 h after PGD diagnosis							
PaO_2/FiO_2	309 (72)	242 (33)	250 (39)	0.002	0.002	0.002	0.261
PCO_2, mmHg	45 (7)	43 (8)	42 (5)	0.070	0.070	0.080	0.089
pH	7.33 (0.48)	7.37 (0.38)	7.40 (0.46)	0.708	0.680	0.783	0.567
Cycles, n (%)	1 [1-2]	2 [1-2]	-	0.491	-	-	-
Duration, h	16 [12-18]	16 [14-18]	-	0.197	-	-	-

Data are expressed as number (percentage), median [interquartile range], or mean (standard deviation). Baseline ABG was defined as the worst sample collected during the first 24 hours after ICU admission. Moreover, the ABGs collected before prone positioning are reported, showing no differences between baseline parameters and those collected before prone positioning.

Abbreviations: ABG, arterial blood gas analysis; Crs, compliance respiratory system; DP, driving pressure; ICU, intensive care unit; $PaCO_2$, arterial carbon dioxide pressure; PaO_2/FiO_2, ratio between arterial oxygen partial pressure and inspiratory oxygen fraction; PGD, primary graft dysfunction.

* p-value not significant.

compared with the late PP group (242 ± 33 mmHg and 53 ± 49, respectively) and the supine group (250 ± 39 mmHg and 31 ± 70 mmHg, respectively) (p = 0.002 and 0.003, respectively) (see Tables 2 and 3 and Fig 3).

Moreover, as shown in Figure 3, the $\Delta PaO_2/FiO_2$ collected at the end of pronation is linearly correlated with the $\Delta PaO_2/FiO_2$ at 12 hours after resupination both in the early PP group (r = 0.63, p = 0.001) and late PP group (r = 0.78, p = 0.001).

Discussion

In the present study, the effect of PP was analyzed in 67 adults undergoing bilateral LT to manage refractory hypoxemia due to PGD grade 2 or 3. Compared with late PP (after 24-48 hours after diagnosis), early PP (within 24 hours from diagnosis) seems to be associated with greater 28-day ventilator-free days (in particular, due to shorter IMV), better oxygenation (either during PP or after resupination) due to a higher increase in PaO_2/FiO_2 from baseline, and improved DP and Crs after PP. Moreover, LT recipients who are turned prone early show greater values of PaO_2/FiO_2 at 72 hours after PGD diagnosis, despite similar 28-day ventilator-free days compared with supine patients.

PGD is the most frequent cause of hypoxemia in the early period after LT and remains a major challenge in the perioperative course, being associated with significant morbidity and mortality.[2,3] Based on strong evidence in the field of ARDS, where PP proved to ameliorate oxygenation and improve long-term survival,[6,11,26] thanks to the recruitment of dorsal lung regions[6,11] and the increase of ventilation-perfusion matching,[10-12] PP has recently been proposed as a safe and low-cost therapy to treat patients with refractory hypoxemia after LT.[8,9,10,27] In a prospective study by Riera and colleagues, 22 LT patients underwent PP after surgery, experiencing a significant increase in PaO_2/FiO_2.[9] Likewise, Frick and coworkers retrospectively investigated a single-center cohort of 165 patients who were turned prone for a median of 19 hours because of impaired primary graft function after LT and reported a significant improvement of oxygenation and pulmonary compliance during PP.[8]

Some important differences must be underlined between these studies and the present work. First, in contrast to the current paper, where PP was reserved only for LT recipients

Table 3
Changes in Arterial Blood Gases Compared With Baseline Values

Outcomes	Early PP, N = 24 (36)	Late PP, N = 18 (27)	Supine Position, N = 25 (37)	Overall p-Value	Early PP *v* Late PP	Early PP *v* Supine	Late PP *v* Supine
$\Delta PaO_2/FiO_2$, mmHg (change from baseline ABG)							
At end of prone positioning	124 (64)	50 (66)	-	-	0.018	-	-
12 h after resupination	124 (84)	40 (63)	-	-	0.016	-	-
72 h after PGD diagnosis	105 (79)	53 (49)	31 (70)	0.003	0.015	0.001	0.159
$\Delta PaCO_2$, mmHg (change from baseline ABG)							
At end of prone positioning	−4 (12)	6 (14)	-	-	0.069	-	-
12 h after resupination	−4 (7)	4 (15)	-	-	0.096	-	-
72 h after PGD diagnosis	3 (7)	6 (12)	-5 (16)	0.116	0.163	0.684	0.134

Data are presented as mean (standard deviation). Baseline ABG was defined as the worst blood sample collected during the first 24 hours after intensive care unit admission.
Abbreviations: ABG, arterial blood gas; FiO_2, inspired fraction of oxygen; $PaCO_2$, carbon dioxide pressure; PaO_2, arterial oxygen partial pressure; PGD, primary graft dysfunction.

suffering moderate-to-severe PGD, the etiology of hypoxemia was heterogenous in other studies. Indeed, while PGD was the most frequent cause of hypoxemia in the experience documented by Riera et al.,[9] in work by Frick et al., PP was considered independent from PGD, and in all cases of PaO_2/FiO_2 <250 mmHg, signs of pulmonary edema at bronchoscopy at the end of transplant, and/or evidence of reperfusion injury at chest x-ray.[8] Second, the timing of PP is difficult to compare among the mentioned studies: different from the current work, where enrolled patients were turned prone within 48 hours from the diagnosis of PGD, Frick et al. investigated only LT recipients treated with PP in the first 12 hours after surgery,[8] while Riera and coworkers also included patients who were turned prone later than 72 hours after LT.[9] Third, none of the previous studies analyzed the effect of PP timing on patient's outcomes. Indeed, to the best of our knowledge, the present study is the first to investigate the best timing for performing PP and suggest a relevant association between early PP and better short-term outcomes in LT recipients developing moderate-to-severe PGD.

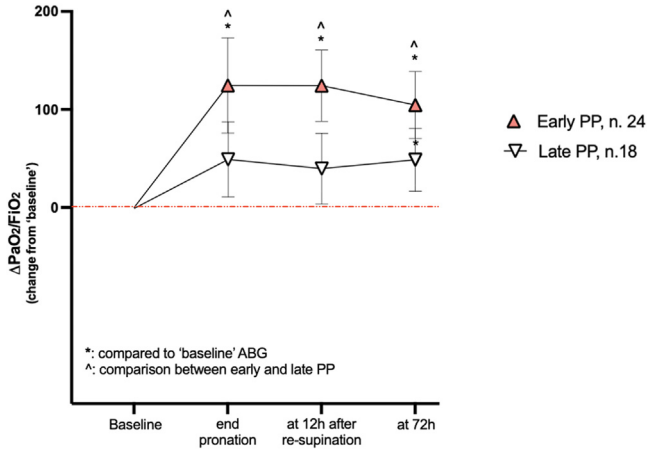

Fig 2. $\Delta PaO_2/FiO_2$ at the end of PP, 12 hours after resupination, and 72 hours later. Data are shown as mean and 95% CI. *Red triangles* represent the early PP group, while *white triangles* represent the late PP group. Baseline was defined as the worst ABG collected during the first 24 hours after ICU admission (before PP). ABG, arterial blood gas; CI, confidence interval; FiO_2, fractional inspired oxygen; PaO_2, arterial oxygen partial pressure; PP, prone positioning.

Although the present work did not aim to ascertain the physio-pathological mechanisms underlying this timing-related improvement, several studies on acute respiratory failure demonstrated that PP reduces both overdistension in non-dependent lung regions and cyclical airspace opening and closing in dependent regions,[12,21,28] which are recognized as major determinants of ventilator-induced lung injury.[29-31] Therefore, since ventilator-induced lung injury may affect clinical outcomes of all patients receiving ventilator support, even outside the clinical scenario of acute respiratory failure and ARDS,[31,32] the current findings seem to encourage the early application of prone ventilation to prevent further complications due to mechanical ventilation and PGD worsening. Indeed, in the present study, although DP and Crs before PP were similar between the early PP and late PP groups, once returned supine after PP, patients in the early PP group showed lower DP and higher Crs. These findings could suggest that early PP may improve lung-protective ventilation and consequently limit ventilator-induced lung injury.

Moreover, it can be speculated that, similarly to ARDS,[11,26,28] in the case of PGD, pulmonary edema, and lung derecruitment are prominent during the early stage of the disease, in the absence of irreversible structural changes; thus the beneficial effects provided by PP are most likely greater and more advantageous than those provided in the late phase when definitive graft damage has already been established.[33,34] In the present experience, despite patients being turned prone at least within 48 hours from the diagnosis of PGD, the only patients who did not experience benefits in terms of PaO_2/FiO_2 after PP were all in the late PP group, while the entire early PP group were prone responders in terms of oxygenation. These results, together with the significant increase in both PaO_2/FiO_2 and $\Delta PaO_2/FiO_2$ in patients turned prone early, seem to highlight the role of PP timing in the reversibility of lung damage due to PGD.

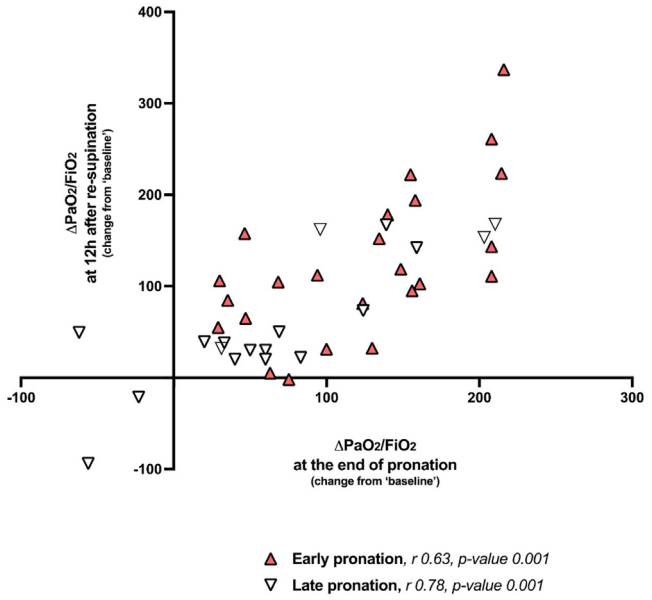

Fig 3. Correlation between $\Delta PaO_2/FiO_2$ at the end of pronation and $\Delta PaO_2/FiO_2$ at 12 hours after resupination. *Red triangles* represent the early PP group, and *white triangles* represent the late PP group. The mean change in PaO_2/FiO_2 refers to the baseline ABG, defined as the worst ABG collected during the first 24 hours after ICU admission. ABG, arterial blood gas; FiO_2, fractional inspired oxygen; PaO_2, arterial oxygen partial pressure; r, Spearman's correlation coefficient.

The present study has some limitations. First, it is a single-center pilot study with both prospective and retrospective cohorts, bearing all the limitations of this research design. Second, the sample size is limited. Therefore, we cannot exclude that the study may be underpowered to detect all clinically relevant differences. Third, the current authors focused on the PaO_2/FiO_2 ratio as a basis for PGD diagnosis and respiratory mechanics measured during ICU stay, while intraoperative data, hemodynamic status (ie, the functionality of the right ventricle, vasoactive and inotropic pharmacological support, volume status, and fluid balance), and different degrees of deterioration and hypoxemia before PP were only marginally considered; therefore, we cannot exclude that these factors may have played a role in the development and evolution of graft damage. For this reason, the results should be considered with caution and must be confirmed by multicenter randomized controlled trials. However, the propensity score–weighting analysis achieved adequate covariate balance among intervention groups and accounted for reasonable confounding in this study design, while maintaining a similar sample size between unbalanced and balanced groups. Fourth, since turning critically ill patients is demanding, particularly in the early post-transplant period,[35] PP obviously requires trained personnel and may lead to serious complications, especially in inexperienced hands.[6,11] The application of this protocol with routine PP of LT patients with PGD may not be feasible in low-experience or low-volume centers. Fifth, PP is not free from possible complications (mainly pressure ulcers and wound dehiscence requiring surgical revisions). Still, its potential benefits on gas exchange, hypoxemia, and length of IMV promote its use. Lastly, long-term outcomes were not investigated.

Conclusion

In conclusion, in this pilot study enrolling 67 bilateral LT recipients with refractory hypoxemia due to moderate-to-severe PGD, turning patients prone early, within 24 hours after diagnosis, seems to be associated with greater 28-day ventilator-free days, better oxygenation, and improved DP and Crs compared with late PP (between 24 and 48 hours after diagnosis). Moreover, LT recipients that are turned prone early show greater PaO_2/FiO_2 value at 72 hours after PGD diagnosis, despite similar 28-day ventilator-free days, compared with supine patients. However, these results must be confirmed by larger multicenter randomized trials.

Meeting Presentation

This work was presented as an abstract at the I-Care meeting (Naple, October 2024).

Central message: In the case of moderate-to-severe PGD, early PP may be a promising maneuver for treating moderate-to-severe hypoxemia and improving outcomes.

Institutional Review Board

Reference 4539/AO/18; informed consent was obtained from all participants.

Perspective Statement

Key question: Does early PP, a rescue maneuver for hypoxemia, improve outcomes after LT with moderate-to-severe PGD?

Key findings: Early PP was associated with greater 28-day ventilator-free days, oxygenation, and gas exchanges than late PP.

Conclusions: In the case of moderate-to-severe PGD, early PP may be a promising maneuver for treating moderate-to-severe hypoxemia and improving outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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– original draft, Formal analysis, Data curation. **Carlo Alberto Bertoncello:** Writing – original draft, Formal analysis, Data curation. **Mario Roccaforte:** Writing – original draft, Formal analysis, Data curation. **Francesco Zarantonello:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Paolo Persona:** Writing – review & editing, Formal analysis, Data curation. **Enrico Petranzan:** Formal analysis, Data curation, Conceptualization. **Gabriella Roca:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Eugenio Biamonte:** Methodology, Data curation, Conceptualization. **Michele Carron:** Writing – original draft, Methodology, Data curation, Conceptualization. **Andrea Dell'Amore:** Writing – review & editing, Data curation, Conceptualization. **Federico Rea:** Writing – review & editing, Supervision, Conceptualization. **Annalisa Boscolo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Paolo Navalesi:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2024.11.018.

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