The role of mechanical ventilation in primary graft dysfunction in the postoperative lung transplant recipient: A single center study and literature review

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Abstract
Background: Primary graft dysfunction (PGD) is still a major complication in patients undergoing lung transplantation (LTx). Much is unknown about the effect of postoperative mechanical ventilation on outcomes, with debate on the best approach to ventilation.

Aim/Purpose: The goal of this study was to generate hypotheses on the association between postoperative mechanical ventilation settings and allograft size matching in PGD development.

Method: This is a retrospective study of LTx patients between September 2011 and September 2018 (n = 116). PGD was assessed according to the International Society of Heart and Lung Transplantation (ISHLT) criteria. Data were collected from medical records, including chest x-ray assessments, blood gas analysis, mechanical ventilator parameters and spirometry.

Results: Positive end-expiratory pressures (PEEP) of 5 cm H₂O were correlated with lower rates of grade 3 PGD. Graft size was important as tidal volumes calculated according to the recipient yielded greater rates of PGD when low volumes were used, a correlation that was lost when donor metrics were used.

Conclusion: Our results highlight a need for greater investigation of the role donor characteristics play in determining post-operative ventilation of a lung transplant recipient. The mechanical ventilation settings on postoperative LTx recipients may have an implication for the development of acute graft dysfunction. Severe PGD was associated with the use of a PEEP higher than 5 and lower tidal volumes and oversized lungs were associated with lower long-term mortality. Lack of association between ventilatory settings and survival may point to the importance of other variables than ventilation in the development of PGD.

KEYWORDS
lung transplant recipients, postoperative mechanical ventilation, primary graft dysfunction, protective lung ventilation
1 | INTRODUCTION

Sixty years of lung transplantation (LTx) have led to the advancement of surgical and perioperative techniques, and yet the procedure remains hindered by a high risk of mortality and morbidity. The complications of LTx can be traced back both to primary graft dysfunction (PGD) and chronic lung allograft dysfunction (CLAD). The consideration of these complications is important in the light of a mere 59% survival rate 5 years following transplantation.2

PGD is acute graft dysfunction in the 72 h following LTx and is graded by the severity of the decrease in the PaO2/FiO2 ratio concomitant with the appearance of infiltrate on chest imaging.3 Grade 3 or severe PGD has an impact on early mortality and is associated with CLAD.4-7 CLAD, marked by a persistent decrease in FEV1, arises in 35% of LTx patients after 5 years and contributes to the overall 27% survival rate 10 years after transplant.8 Interventions that reduce the rate of PGD could thus have consequences for both the short-term and long-term outcomes of LTx patients. All-cause mortality within the first 30 days following the transplantation can be influenced by the incidence of PGD, as a study on over 5,000 patients across an international registry found that those with PGD had a 42.1% 30-day mortality rate relative to the 6.1% in those without.5

While a singular etiology of PGD is yet unproven, there are a number of known factors correlated with PGD, including increasing donor age and smoking history.9 Given the potential role of ischemia-reperfusion injury as well as the risk of ventilatory induced lung injury (VILI), settings for mechanical ventilation must be carefully considered.10,11 The optimization of size matching may also be a factor in reducing rates of PGD as stress and over-distension of alveoli lead to VILI.12

PGD has been shown to be clinically and histologically analogous to acute respiratory distress syndrome (ARDS)13,14 and so discussion has grown regarding the application of established ARDS protective ventilation strategies to prevent PGD. Protective ventilation refers to the use of a low tidal volume of 6 ml/kg.15,16

A mismatch in lung sizes between the donor and the recipient could lead to undersized allografts receiving relatively higher tidal volumes when calculated according to the donor’s predicted body weight (donor PBW).17 As larger tidal volumes are associated with an increased risk of development of ARDS18 and due to the parallels between ARDS and PGD, tidal volumes when calculated according to the recipient rather than the donor could impact the development of PGD.

An international survey conducted by Beer et al19 demonstrated that the majority of practitioners consider only the recipient’s PBW when setting either volume or pressure-assisted ventilation. 58% of respondents did not even have donor information. The codification of guidelines for mechanical ventilation could lead to a decrease in the rates of allograft dysfunction. This study aims to determine the role of considering both donor and recipient characteristics when determining ventilation settings and the relationships of these factors to PGD.

2 | METHODS

2.1 | Patients

This retrospective study includes all LTx recipients at the Department of Cardiothoracic Surgery, Anaesthesia and Intensive Care Unit at Lund University Hospital in Lund, Sweden, between September 2011 and September 2018 (n = 116). The study was approved by the local ethical committee (Dnr 2016/638). Recipients and donors were approved for transplantation by our standard clinical routine, in line with latest guidelines.20

PGD was defined and classified as grade 0, 1, 2, or 3 according to the ISHLT definition3 as outlined in Table 3. The definition is reached upon evaluation of chest X-ray, blood gases (partial pressure of oxygen in arterial blood, PaO2) and oxygen concentration in inhaled air (FiO2). PGD was evaluated every 24 h during the first 72 h post-operatively. Chest X-rays were assessed by a clinical radiologist for evaluation of the presence of infiltrates and/or pulmonary edema.

Patients treated with postoperative ECMO were classified as grade 3 PGD.

2.2 | Postoperative management and mechanical ventilation

Patients were admitted to the intensive care unit (ICU) designated specifically for cardiothoracic surgical patients wherein each patient received tailored care by a cardiothoracic anaesthesiologist for their postoperative care. All patients in this study were ventilated using a Servo-1 Ventilator (Getinge AB, Gothenburg, Sweden) under the pressure-regulated-volume-controlled (PRVC) mode. Due to the unique challenges that each transplant recipient faces, guidelines are in place with a goal of ventilating at 5–6 ml/kg calculated according to
the recipient with a PEEP of 5 and plateau pressure less than 30 cm H$_2$O but ventilatory measures are adjusted according to regular blood gas measurements and clinical evaluation by the attending anaesthesiologist. The patient is kept at a head elevation of 30° to unload the right heart chamber for the prevention of right heart failure. The attending physician used the recipient characteristics to determine appropriate ventilatory settings at the time of admission to the ICU. Ventilatory settings and measures in this study were collected and a positive end-expiratory pressure (PEEP) and a driving pressure were analyzed. The guideline aim was to maintain a PEEP of 5, and the study data categorized patients as either PEEP of 5 or a PEEP greater than 5. However, there were 6 patients who were ventilated at times with pressures less than 5 due to clinical concerns, such as right heart failure and concern over air leakage, but were still included in the analysis. Lung protective ventilation was in this study defined as low tidal volume (≤6 ml/kg), and was calculated on the basis of the donor and the recipient. Patients were then determined to be protectively ventilated relative to the tidal volume for the recipient or the donor.

### 2.3 | Graft mismatch

A predicted total lung capacity (pTLC) was calculated based on sex, age, and height as described by Eberlein et al.$^{22}$:

$$\text{pTLC for male} = 0.08 \times [\text{Height in cm}] + 0.003 \times [\text{age in years}] - 7.333$$

| Variable                        | T0            | T24           | T48           | T72           |
|---------------------------------|---------------|---------------|---------------|---------------|
| **Recipient demographics**      |               |               |               |               |
| Sex; Female                     | 57 (49.1%)    |               |               |               |
| Age at LTx, years               | 53.7 (60.7–42.4) |       |               |               |
| Height, cm                      | 170.7 ± 9.3   |               |               |               |
| Weight, kg                      | 66.8 ± 17.3   |               |               |               |
| BMI, kg/m$^2$                   | 22.8 ± 5.0    |               |               |               |
| Pediatric LTx, age <18 years    | 2 (1.7%)      |               |               |               |
| **Diagnosis**                   |               |               |               |               |
| COPD/Emphysema/A1ATD            | 40 (34.5%)    |               |               |               |
| Cystic Fibrosis                 | 22 (19.0%)    |               |               |               |
| IPF/PF specified                | 24 (20.7%)    |               |               |               |
| Other (PPH, Sarcoidosis)        | 30 (25.9%)    |               |               |               |
| **Single LTx**                  | 9 (7.8%)      |               |               |               |
| **Lung Retransplantation**      | 7 (6.0%)      |               |               |               |
| **ECMO use**                    | 11 (9.5%)     |               |               |               |
| **Preoperative**                | 4 (3.4%)      |               |               |               |
| **Postoperative**               | 11 (9.5%)     |               |               |               |
| **Ventilator Characteristics**  |               |               |               |               |
| FiO$_2$                         | 0.47 ± 13     | 0.36 ± 10     | 0.32 ± 07     | 0.33 ± 11     |
| Tidal volume (ml)               | 448 ± 83      | 465 ± 101     | 451 ± 104     | 455 ± 130     |
| **Donor demographics**          |               |               |               |               |
| Sex; Female                     | 67 (57.8%)    |               |               |               |
| Age, years                      | 54.0 (63.0–40.0)|        |               |               |
| Age <18 years                   | 6 (5.2%)      |               |               |               |
| Height, cm                      | 170.5 ± 8.9   |               |               |               |
| Weight, kg                      | 74.2 ± 15.1   |               |               |               |
| BMI, kg/m$^2$                   | 25.4 ± 4.0    |               |               |               |
| Days on MV                      | $\bar{x} = 1.65$ (3–1) |       |               |               |
| LOS in ICU                      | $\bar{x} = 7$ (17.75–5) |       |               |               |
| Reintubated                     | 36 (31.0%)    |               |               |               |
| Return to ICU                   | 24 (20.7%)    |               |               |               |

Note: Numbers are expressed as the mean $\bar{x} \pm$ SD (when parametric), median $\bar{x}$ (interquartile range) or numerical values (%). Abbreviations: A1ATD, α-1-antitrypsin deficiency; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; FiO$_2$, fraction of inspired oxygen; IPF, Idiopathic Pulmonary Fibrosis; LTx, Lung transplantation; PF, Pulmonary fibrosis; PPH, primary pulmonary hypertension; T0, time of admission to the ICU; T24, 24 h after admission; T48, 48 h after admission; T72, 72 h after admission.
TABLE 2 Intraoperative characteristics (n = 116)

| Variable                  |           |
|---------------------------|-----------|
| Intraoperative machine perfusion |          |
| ECMO                      | 28 (24.1%)|
| Average time, minutes     | 371 ± 135 |
| ECC                       | 67 (57.8%)|
| Average time, minutes     | 223 ± 67  |
| Off-pump                  | 20 (17.2%)|

Ischemic time

| Right Lung, minutes       | 236 ± 103 |
| Left Lung, minutes        | 281 ± 103 |

Note: Numbers are expressed as the mean ± SD (when parametric), median (interquartile range) or numerical values (%). ECMO = extracorporeal membrane oxygenation, ECC = extracorporeal circulation. Off-pump refers to patients in whom extracorporeal circulation was not used. Ischemic time was defined as the time from clamp on the donor to the time of reperfusion in the recipient.

TABLE 3 Grading of primary graft dysfunction according to the definition from the International Society of Heart and Lung transplantation (2016)

| Grade | Pulmonary Edema on chest X-ray | PaO2/FiO2 ratio |
|-------|---------------------------------|-----------------|
| 0     | No                              | Any             |
| 1     | Yes                             | >300            |
| 2     | Yes                             | 200–300         |
| 3     | Yes                             | <200            |

pTLC for female = \(0.059 \cdot x [\text{Height in cm}] - 4.537\)

A pTLC ratio was calculated as donor pTLC / recipient pTLC. Grafts were said to be matched if the ratio was between 0.95–1.05. Grafts with a ratio <0.95 were labeled undersized while those >1.05 were oversized.

2.4 Data collection

Data were extracted from medical record systems; Intellispace critical care and anaesthesia (ICCA, Koninklijke Philips electronics N.V. Amsterdam, the Netherlands) and Melior (Siemens AB, Healthcare service, Solna, Sweden). Mechanical ventilator settings, blood gas samples and chest x-ray results were analyzed at five different time points: preoperatively, on arrival in the ICU, the following morning at 6am, and the two consecutive mornings after. Last day for follow-up was July 23, 2020.

2.5 Statistical analysis

Categorical variables were presented as numbers (%) and continuous variables were presented as the mean ± SD for parametric data or median (interquartile range) for non-parametric data. Incidence of PGD was analyzed using the independent sample t-test for continuous parametric variables, chi^2 and Fisher’s exact test (when expected frequency <5) for categorical variables. For non-parametric continuous variables, the Mann–Whitney u-test and Kruskal–Wallis H test were applied. Within PGD groups, statistically significant differences were analyzed using a z-test run with Bonferroni correction. Survival analysis was determined in a time-related manner with the Kaplan–Meier method and differences between groups were analyzed using the Log-rank test. Statistical significance was defined as \(p < .05\). All statistical calculations were performed using SPSS Statistics 26 (IBM Corp., Armonk, NY, US).

3 RESULTS

3.1 Patient demographics

Table 1 shows patient characteristics. 49.1% of recipients were female and had a median age of 53.7 years (IQR 60.7–42.4). 92.2% of patients received a double lung transplant and stayed in the ICU for a median of 7 days (IQR 17.75–5). The median number of days on mechanical ventilation was 1.65 (IQR 3–1). Thirty-six patients (31.0%) were reintubated while 24 (20.7%) returned to the ICU during their hospital stay.

3.2 PGD

Within the first 72 h of their stay in the ICU, 18 patients did not develop any PGD, while 50 developed PGD grade 1 or 2 and 47 developed grade 3 PGD. Those who developed PGD were more likely to have a higher BMI (\(p = .003\)) and an older donor age was correlated with the development of PGD (\(p = .011\)), but other general recipient and donor demographics demonstrated no difference. There were no significant differences in the frequency of PGD among different diagnoses nor were there differences between the length of stay in the ICU, rates of reintubation, return to the ICU or days spent on ventilation.

When considering PEEP, there was a significant difference between the 21.3% of grade 3 PGD patients who received PEEP of 5 cm H2O and the 53.2% who were PGD grade 1 or 2 with this PEEP (\(p = .006\)). There was a smaller proportion of grade 3 PGD on PEEP of 5 than the 38.9% of grade 0.

In patients whom driving pressure was kept at less than 20 cm H2O, there was a lower rate in those who developed PGD 3 (48.9%) relative to those with PGD grades 1 or 2 (66.0%) or no PGD (61.1%). While not statistically significant, the data shows a trend of the more severe dysfunction grade being composed more predominantly of patients with higher driving pressure values.

Tidal volumes were calculated either according to the recipient’s demographics or according to the donor’s, as shown in Tables 4 and 5. When calculated with respect to the recipient, it was found that relative to the group without PGD or to the group with grades 1 or 2, those with grade 3 PGD were made of a significantly greater proportion of individuals receiving a tidal volume ≤6 ml/kg (\(p = .037\)). When
calculated according to the donor, there were no significant differences between any of the groups. The average tidal volume at the time of admission to the ICU was 448 ± 83 ml, and was 465 ± 101 ml after 24 h, 451 ± 104 ml at 48 h, and 455 ± 130 ml at 72 h.

The pTLC ratio compares the donor lung capacity to that of the recipient. Among those whose graft was considered “matched,” 21.4% had no PGD while 33.3% experienced either grade 1 or 2 and 45.2% experienced grade 3 PGD (Figure 1A). In the undersized category, only 15.8% did not have PGD while 47.4% had grade 1 or 2 and 36.8% had grade 3 (Figure 1A). Lastly only 8.6% with oversized grafts had no PGD and 36.0% had grade 1 or 2 and 29.8% had grade 3 (Figure 1A).

### Table 4: Development of primary graft dysfunction at any time during the first 72 h after lung transplantation $n = 115$

| Variable                        | No PGD $n = 18$ | PGD Grade 1 or 2 $n = 50$ | PGD Grade 3 $n = 47$ | $p$-value |
|---------------------------------|-----------------|---------------------------|----------------------|----------|
| **Recipient demography**        |                 |                           |                      |          |
| Female gender                   | 8 (44.4%)       | 24 (48.0%)                | 24 (51.1%)           | .885     |
| Age at LTx, years               | 49.1 (25.0–61.3)| 55.5 (45.5–62.0)          | 52.7 (37.4–60.0)     | .167     |
| BMI, kg/m²                      | 19.8 ± 4.6      | 22.4 ± 4.6                | 24.4 ± 4.9           | .003     |
| **Donor demography**           |                 |                           |                      |          |
| Female gender                   | 8 (44.4%)       | 28 (56.0%)                | 30 (63.8%)           | .355     |
| Age, years                      | 42.5 (23.0–56.2)| 52.5 (40.8–65.3)          | 57.0 (46.0–69.0)     | .011     |
| **Diagnosis**                   |                 |                           |                      |          |
| COPD/Emphysema/A1ATD            | 6 (33.3%)       | 22 (44.0%)                | 12 (25.5%)           | .160     |
| Cystic fibrosis                 | 6 (33.3%)       | 8 (16.0%)                 | 7 (14.9%)            | .195     |
| IPF/PF specified                | 1 (5.6%)        | 11 (22.0%)                | 12 (25.5%)           | .201     |
| Other                           | 5 (27.8%)       | 9 (18.0%)                 | 16 (34.1%)           | .195     |
| **Ventilatory Pressures**       |                 |                           |                      |          |
| PEEP of 5 cm H₂O until T72      | 7 (38.9%)       | 25 (53.2%)                | 10 (21.3%)           | .006     |
| Driving Pressure <20 until T72  | 11 (61.1%)      | 31 (66.0%)                | 23 (48.9%)           | .210     |
| **Tidal Volume ≤6 ml/kg**       |                 |                           |                      |          |
| With respect to recipient until T72 | 3 (16.7%) | 9 (19.1%)                 | 19 (41.3%)           | .037     |
| With respect to donor until T72 | 8 (44.4%)       | 21 (44.7%)                | 20 (43.5%)           | .977     |
| **Tidal Volume >6 ml/kg**       |                 |                           |                      |          |
| With respect to recipient until T72 | 15 (83.3%) | 38 (80.9%)                | 28 (59.7%)           | .037     |
| With respect to donor until T72 | 10 (55.5%)      | 26 (55.3%)                | 26 (55.6%)           | .977     |
| **pTLC ratio 5%**               |                 |                           |                      |          |
| Undersized                      | 6 (33.3%)       | 18 (36.0%)                | 14 (29.8%)           | .809     |
| Perfect match                   | 9 (50.0%)       | 14 (28%)                  | 19 (40.4%)           | .193     |
| Oversized                       | 3 (16.7%)       | 18 (36.0%)                | 14 (29.8%)           | .308     |
| Days on MV                      | 2.1 ± 2.2       | 4.0 ± 8.2                 | 8.3 ± 14.9           | .066     |
| LOS in ICU                      | 11.9 ± 11.8     | 15.2 ± 19.0               | 18.6 ± 22.4          | .440     |
| Re-intubated                    | 2 (11.1%)       | 18 (36.7%)                | 16 (35.6%)           | .113     |
| Return to ICU                   | 4 (22.2%)       | 7 (14.3%)                 | 13 (28.9%)           | .225     |

Note: Numbers are expressed as the median (interquartile range), mean ± SD (when parametrical) or numerical values (%). Level of significance is defined as $p < .05$. Abbreviations: A1ATD, alfa-1-antitrypsin deficiency; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; IPF, Idiopathic Pulmonary Fibrosis; LOS, Length of stay; Lx, Lung transplantation; MV, Mechanical Ventilation; PGD, Primary graft dysfunction; PF, Pulmonary fibrosis; PEEP, positive end expiratory pressure; pTLC, predicted total lung capacity; T72, 72 h post operatively.

* = between group difference $p < .05$ using a z-test ran with Bonferroni correction.
3.3 | Survival

Sixty-three of the patients (54.3%) were alive at the last date of follow-up, compared to 53 (45.7%) who had passed.

When examining PEEP values, driving pressures and tidal volumes, these parameters were not statistically significantly different in survivors versus non. There were also no significant differences in the survival rates between the three groups of PGD. However, there

### TABLE 5 Values of ventilation parameters and ischemic times n = 115

| Variable                                | No PGD n = 18 | PGD Grade 1 or 2 n = 50 | PGD Grade 3 n = 47 |
|-----------------------------------------|---------------|-------------------------|-------------------|
| Ventilatory parameters                 |               |                         |                   |
| Tidal volume ml per kg of recipient    | 7.97 ± 1.63   | 7.19 ± 1.86             | 6.73 ± 2.08       |
| Tidal volume ml per kg of donor        | 6.32 ± 1.78   | 6.45 ± 1.37             | 5.76 ± 1.87       |
| PEEP                                    | 5.68 ± 1.09   | 5.21 ± 0.92             | 6.00 ± 1.57       |
| Driving pressure                        | 9.93 ± 5.92   | 16.37 ± 37.64           | 13.08 ± 5.66      |
| Ischemic time of left lung (min)       | 222.1 ± 67.22 | 282.4 ± 95.39           | 299.7 ± 113.6     |
| Ischemic time of right lung (min)      | 238.2 ± 107.1 | 243.1 ± 96.06           | 232.0 ± 105.7     |

Note: Numbers are expressed as the mean ± SD.

Abbreviations: PEEP, positive end expiratory pressure; PGD, Primary graft dysfunction.

### FIGURE 1 PGD Incidence Correlated to Size Matching of the Graft

Grafts were defined as undersized when the predicted total lung capacity (pTLC) ratio of donor to recipient was less than 0.95. Matched grafts were considered to be those in the ratio range of 0.95–1.05 while values above 1.05 were allocated as oversized. Both undersized and oversized grafts (A) had a trend of slightly PGD grade 1 or 2 and grade 3 relative to matched grafts. The relationship between size matching and graft dysfunction was then also considered specifically among those patients who received a tidal volume less than 6 ml/kg when calculated according to the donor (B). *p < .05, **p < .01. PGD, primary graft dysfunction.
was a tendency for lower survival in PGD grade 3 compared to the other groups (Figure 2). The size of the graft, however, was a significant factor in survival. Of those patients who were deceased, 47.2% were considered to have a strict match (the pTLC ratio was between 0.95 and 1.05) while 20.8% had oversized grafts, meaning a graft with a ratio greater than 1.05 (Table 6). In the patients that lived, only 27.0% of them had matched grafts while 39.7% had oversized grafts. In patients with matched pTLC ratios, the number deceased was significantly higher than those who survived ($p = .024$) and in patients with oversized ratios, the number of deceased was significantly lower than those who survived ($p = .028$).

When analyzing the survival rates, it was determined that the effect of graft size on survival was most apparent in COPD/emphysema/A1ATD patients in whom there was a significantly increased number of surviving oversized grafts relative to matched grafts that died ($p = .019$). Of those with COPD who survived, 61.1% had oversized grafts while in the deceased patients, 54.5% had matched grafts (Figure 3).

### DISCUSSION

A relationship between mechanical ventilation of lung recipients and the development of severe PGD may exist, but the current associations discussed here are hypothesis generating. In this study, in all the individuals who did develop grade 3 dysfunction, 78.7% of those were patients who had been ventilated with a PEEP higher than 5 cm H$_2$O (Figure 4A, Table 4). Given the association between a PEEP of 5 and lower PGD in this study, it might be favorable to apply a pressure that allows for patency of the alveoli and lung protection while taking into account the loss of bronchial circulation of a new transplant. Furthermore, while not statistically significant, the same pattern was observed regarding driving pressure. There should be further investigation as to the causation of how and why higher proportions of patients with grade 3 PGD correlated with higher pressure settings.
The rationale for such investigation lies in the evidence that ischemia-reperfusion injury can lead to pulmonary edema and diffuse alveolar damage and may have a central role in the development of PGD. Additionally, greater capillary stress in the face of size mismatch is hypothesized to be a potential mechanism to explain the incidence of PGD in single LTx. Stress and over-distending alveoli may also lead to ventilator-induced lung injury, which could occur with high levels of PEEP and peak inspiratory pressures.

Size matching is recognized as an important parameter of consideration during lung transplantation. As noted by the ISHLT, while the graft size is a crucial factor in organ donation acceptance, the topic is a yet under-investigated subject. In this study, oversized grafts were found to be advantageous to survival, particularly in patients with a diagnosis of COPD, emphysema, or alpha-1 antitrypsin deficiency. Predicted total lung capacity ratios were used to compare the donor size to the recipient and strict criteria were employed to consider any graft that was above 5% larger than the recipient to be oversized. In a study of donor-to-recipient weight ratio, Delom et al. found that a higher ratio was associated with improved survival following bilateral transplantation, accounting for this by pointing to the likely size mismatch between donor and recipient. Furthermore, Shaffer et al. found that among transplants in COPD patients, oversized grafts measured by pTLC ratio ≥1 were associated with survival. Eberlein et al. also found that oversized grafts corresponded with lower rates of BOS and higher expiratory airflow capacity after measuring size matching using pTLC ratios.

Another critical ventilatory parameter to consider is tidal volume given existing debate on the use of either recipient or donor characteristics. Currently, many institutions measure relative to the recipient, but the data presented here makes an argument that donor demographics should be used instead. When looking...
at the low tidal volume measured according to the recipient, which is considered protective in ARDS patients, there were increasing proportions of individuals as PGD grades increased. 16.7% of PGD 0 patients had received low tidal volumes (calculated according to the recipient) compared to the 19.1% of grade 1 or 2 and a larger 41.3% of grade 3 (Table 4). The difference could suggest that when trying to employ protective settings, the dimensions of the recipient could not be conducive to providing adequate ventilation to the newly grafted lungs and if mismatched, could increase the risk of developing a more severe acute graft dysfunction. When the tidal volume was calculated according to the donor, however, all differences between the groups were lost (Figure 4C,D, Table 4).

This observation of the effect of tidal volume as measured according to the donor or the recipient could be down to the size of the grafted lung within the recipient and how well they match. Grade 3 PGD patients consisted of either oversized or undersized lungs which made up a combined percentage of 59.6% mismatched lungs compared to the 40.4% that were matched (Figure 1B). In those individuals who are oversized, the larger donor lungs have been placed into a smaller recipient. Thus, it could be hypothesized that by calculating tidal volume according to a recipient, these larger lungs are not getting the adequate ventilation they need. Conversely, by putting smaller donor lungs into a larger recipient and then ventilating according to that larger recipient, damage is induced by overfilling the grafted lungs. In both these cases, by using recipient compared to donor information, damage ensues, leading to acute dysfunction. Decreased tidal volume relative to kilograms of body weight in ARDS patients has translated to decreased mortality and increased number of days without ventilator use, validating the implementation of lung protective ventilation.15

Survival in this study, however, was not found to be affected by low volumes of PEEP, driving pressure, and tidal volumes (Table 6). One limitation of this study is the consideration that as transplantation took place between September 2011 to September 2018, this is a short timeframe to fully understand how mechanical ventilation affects survival. An investigation over a longer patient follow up period will need to be conducted.

Other limitations of this study include emphasis on the hypothesis-generating nature of the associations. The retrospective analysis of a relationship between ventilatory mode and PGD does not allow for conclusions about causal relationships to be drawn. The associations between how ventilation relates to the severity of PGD could be due to the consequence of having more patients with advanced lung dysfunction in the PGD grade 3 group which necessitated ventilation with higher pressures. The choice to ventilate with lower volumes could also have been a measure taken on the part of the anesthesiologist to prevent further damage to already declining lungs. Furthermore, analysis of survival in this study did not reveal an impact on the degree of PGD on mortality, though there was a tendency of lower survival in the PGD grade 3 group. Further study should include a larger number of patients to bolster the power of the study.

The importance of further research on mechanical ventilation settings becomes apparent when considering the current body of literature that exists around our understanding of how to postoperatively ventilate patients. Much of the work that has been done and the recommendations that have been made are based on studies done on ARDS.

In 2000, a landmark study headed up by the ARDS Network used a randomized controlled trial of 861 patients to demonstrate that in the event of pre-existing ARDS, a lower tidal volume was associated with lower mortality rates and a lower number of days without ventilator use.15 The use of mean tidal volumes in the range of 6 ml/kg of predicted body weight (PBW) has subsequently become more common clinical practice in the scope of ARDS treatment, despite some studies with smaller patient groups that have failed to observe a benefit of small tidal volumes.27 In a 2010 investigation into mitigating the risk of developing acute lung injury, Determann et al. explored the use of a low tidal volume of 6 ml/kg of PBW in critically ill patients and found that cytokine levels and the incidence of ALI/ARDS were reduced as compared to conventional tidal volumes.28

Following the logic that low tidal volume may therefore prove beneficial in a lung transplant setting, Mascia et al. in 2010 used low tidal volumes in donor patients in an attempt to increase the number of available organs.29 The number of patients who met donor eligibility criteria had increased in the protective group without any change to six-month survival rates.

Positive end expiratory pressures have also been studied to reduce VILI. As VILI is thought to be a consequence of alveolar stretch secondary to high lung volumes as well as shear stress in opening and closing alveoli,12 PEEP could be used to circumvent collapse of small airways. PEEP has thus been used in patients with ARDS. A study by the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network found no difference in clinical outcomes between the use of low (8 cm H2O) PEEP and high (13 cm H2O) PEEP.30 In a meta-analysis of trials using higher and lower PEEP in response to ALI and ARDS, different PEEP levels were not associated with hospital survival.

While these studies on ARDS provide valuable insight on beginning to create guidelines for lung transplant patients, these two patient populations are not equivalent. Transplant recipients experience significant medical challenges that require careful consideration, such as the risk for ischemia-reperfusion injury, dynamic hyperinflation in emphysematous single transplant patients, and concerns regarding the bronchial anastomoses across all patients.21,21 While studies on ARDS patients can serve as a starting point to begin considering ventilation strategies, there must be independent research on the transplant patient population specifically. The studies that have been conducted on transplant patients are outlined in Table 7.

The ventilation guidelines have been explored to some extent for donor patients. Mascia et al. compared a PEEP of 3–5 cm H2O to a protective group setting of 8–10 cm H2O in donors.29 As noted, there were more available donor lungs in this protective group but no differences in recipient survival. In an intraoperative study of
| Authors                  | Article type                     | Patient population        | Recommendations/Contributions to the literature                                                                                                                                                                                                 | Recommended tidal volume?          |
|-------------------------|----------------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Currey et al. 2009<sup>44</sup> | Prospective single center cohort | Lung transplant recipients | Implementation of a respiratory guideline that advises changing values of PEEP and tidal volume based on categories of PaO<sub>2</sub>/FiO<sub>2</sub> ratios alongside a hemodynamic guideline was associated with a tendency for reduced PGD severity following transplantation. | Dynamic based on patient PaO<sub>2</sub>/FiO<sub>2</sub> |
| Mascia et al. 2010<sup>29</sup> | Randomized Controlled Trial       | Potential Lung Donors     | Tidal volumes of 6–8 ml/kg of predicted body weight, PEEP of 8-10 cm H<sub>2</sub>O led to increased number of patients meeting lung donor eligibility without changing six month survival rates in recipients.                                                                 | 6–8 ml/kg of predicted body weight |
| Diamond et al. 2013<sup>45</sup> | Prospective multicenter cohort   | Lung transplant recipients | In an identification of risk factors associated with PGD across 1,255 recipients, elevated FiO<sub>2</sub> during reperfusion was among the recognized factors. Tidal volume per kg of ideal body weight at reperfusion was not associated and postoperative ventilatory strategies were unable to be assessed. | No                                 |
| Eberlein et al. 2012<sup>46</sup> | Retrospective Single center cohort | Lung transplant recipients | Undersized grafts as determined by a pTLC ratio ≤ 1.0 were associated with higher incidents of PGD, tracheostomy, and greater resource utilization.                                                                                                                              | No                                 |
| Eberlein et al. 2013<sup>47</sup> | Retrospective Single center cohort | Lung transplant recipients | Using the same pTLC ratio organizational scheme, concluded that oversized grafts were associated with improved survival in bilateral LTx in idiopathic pulmonary arterial hypertension patients.                                                                                                        |                                    |
| Dezube et al. 2013<sup>47</sup> | Retrospective single center cohort | Lung transplant recipients | Undersized and oversized grafts as measured by ratio of predicted total lung capacity (pTLC) of donor to pTLC of recipient were compared. Tidal volumes were higher in undersized grafts when tidal volume was calculated by donor-predicted body weight.                                        | Use donor based calculations       |
| Thakuria et al. 2016<sup>48</sup> | Retrospective single center review | Lung transplant recipients | Patients were grouped according to low (<6 ml/kg), medium (6–8 ml/kg) or high (>8 ml/kg) tidal volumes. There was no difference in short-term and midterm outcomes across these groupings. Patients were also categorized by low (<25 cm H<sub>2</sub>O) or high (>25 cm H<sub>2</sub>O) inflation pressures and it was found that the low group had shorter ICU stays, higher FEV1's and higher 6 month survival rate. | <6 ml/kg                           |
| Verbeek et al. 2017<sup>22</sup> | Randomized Controlled Trial       | Intraoperative recipient  | Control group of volume-controlled ventilation with 5 cm H<sub>2</sub>O PEEP and 6 ml/kg tidal volume was compared to an alveolar recruitment group with pressure controlled ventilation at 16 cm H<sub>2</sub>O and 10 cm H<sub>2</sub>O PEEP throughout the duration of surgery. There was no sustained benefit to the "open lung ventilation" strategy. | No                                 |
| Benazzo et al. 2021<sup>49</sup> | Prospective multicenter cohort   | Lung transplant recipients | Ventilatory parameters of donors were prospectively measured at standard 6 ml/kg tidal volume and were correlated to the study end point of recipient time on ventilator to reach the conclusion that donor ventilation may assess graft quality. | No                                 |

(Continues)
| Authors | Article type | Patient population | Review of ARDS/ ALI lit? | Review of transplant recipient ventilation lit? | Recommendations |
|---------|--------------|---------------------|--------------------------|------------------------------------------|------------------|
| Lucangelo et al, 2012 | Review | Donor and recipient postoperative care | Yes | No | Advised to use pressure-controlled ventilation modality with low tidal volumes ($\leq 6 \text{ ml/kg}$), “moderate PEEP levels”, inspiratory pressure less than 20 cm H$_2$O above PEEP, and permissive hypercapnia. Specific recommendations for reperfusion injury and dynamic hyperinflation. |
| Verbeek and Myles, 2013 | Review | Intraoperative recipient | Yes | Yes: Lucangelo, 2012 (review) | Concludes that low tidal volumes have become standard practice and that in regards to other parameters, more research is needed. |
| Bansal et al. 2014 | Review | Potential Lung Donors | Yes | Review is specific to lung donors. | Recommends the use of lung protective ventilatory strategies with “adequate” PEEP levels. |
| Diamond and Ahya, 2014 | Editorial | Lung Transplant Recipients | Yes | Dezube, 2013; Beer, 2014 (survey), Lucangelo, 2012 (review); Verbeek, 2013 (review); Diamond, 2013 | Summarizes the question of using donor and recipient characteristics and comments on the literature of dangers of high FiO$_2$ and potential benefits of high PEEP. |
| Barnes et al. 2015 | Review | Lung transplant recipients | Yes | Cites murine models as well as Currey, 2010; Eberlein, 2013; Eberlein, 2012; Diamond and Ahya 2014 (editorial); and articles on ECMO | Summarizes considerations for bilateral and single lung transplant as well as bronchial anastomoses including references to murine models. Recommends lung protective ventilation defined as tidal volume $\leq 6 \text{ ml/kg}$ and PEEP with ventilation based on donor characteristics. |
| Geube et al 2019 | Review | Lung transplant recipient | Yes | Risk factors for PGD 3 development | Provides a ventilation guideline based on low tidal volume and “optimized” PEEP. |
| Authors               | Article Type                      | Patient Population                  | Recommendations/Contributions to the literature                                                                 |
|----------------------|-----------------------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Tugrul et al. 1997   | Randomized Controlled Trial       | Patients undergoing thoracotomy     | Pressure Controlled Ventilation (PCV) vs Volume Controlled Ventilation (VCV) PCV compared to VCV was superior in the case of respiratory disease. |
| Unzueta et al. 2007  | Randomized Controlled Trial       | Patients undergoing thoracotomy     | PCV provided no benefit in terms of oxygenation compared to VCV during one lung ventilation (OLV).            |
| Roze et al. 2010     | Prospective Observational study   | Patients undergoing thoracotomy     | PCV vs VCV does not have a clinically significant impact on oxygenation in OLV.                              |
| Wrigge et al. 2004   | Randomized controlled trial       | Patients undergoing thoracotomy or laparotomy | “Protective” tidal volumes and PEEP No effect on arterial oxygenation or inflammatory reactions               |
| Choi et al. 2006     | Randomized Controlled Trial       | Patients undergoing at least 5 h of surgery with no prior lung disease | Higher TV and no PEEP led to bronchoalveolar clogulation.                                                  |
| Unzueta et al. 2012  | Randomized controlled trial       | Patients undergoing thoracotomy     | Alveolar recruitment maneuver consisting of 10 consecutive breaths at a plateau pressure of 40 and 20 cm H₂O PEEP OLV, Found alveolar recruitment led to reduced alveolar dead space, improved oxygenation and efficiency of ventilation. |
| Rozé et al. 2012     | Prospective randomized cross-over trial | Patients undergoing thoracotomy     | OLV, High TV and low PEEP had increased oxygenation relative to low TV and high PEEP                           |
| Futier et al. 2013   | Randomized controlled trial       | Intraoperative patients undergoing major abdominal surgery | The protective group was found to have fewer pulmonary complications and required less postoperative ventilatory assistance. |
| Maslow et al. 2013   | Randomized Controlled Trial       | Patients undergoing thoracotomy and pulmonary resection | OLV, High TV and 0 PEEP had less dead space ventilation and postoperative atelectasis                        |
| Gu et al. 2014       | Meta-analysis                     | Patients undergoing surgery         | Lower tidal volumes had a lower risk of lung injury and pulmonary infection                                |
| Qutub et al. 2014    | Randomized controlled trial       | Patients undergoing thoracoscopic surgery | OLV, lower TV was associated with less lung water content                                                   |
mechanical ventilation during transplantation by Verbeek et al. in 2017, patients undergoing bilateral lung transplantation, a control group with a PEEP of 5 had no changes in primary outcomes compared to a PEEP of 10 cm H₂O.32

As there are few studies on transplant recipients specifically, other studies of protective ventilation in surgical procedures, such as abdominal surgery and thoracotomies, are important to consider, as summarized in Table 8. The IMPROVE study demonstrated that intraoperative lung-protective ventilation during abdominal surgery was correlated with lower rates of lung injury when patients were at intermediate to high risk of pulmonary complications.33 Using both low tidal volumes and PEEP, the protective ventilation group was found to have a lower incidence of intubation for ARDS as well as a shorter length of hospital stay.

There are no set standards in ventilation for lung transplant patients. The majority of recommendations for transplantation have been based on the findings from studies that analyzed patients with ARDS and/or acute lung injury. There are a limited number of studies that have been conducted on surgical patients and a similarly limited number on transplantation patients specifically. These studies and their findings have been outlined in Tables 7 and 8. As PGD and chronic dysfunction continue to hamper the survival of LTx patients, there cannot be enough emphasis on how important continued research on mechanical ventilation is.

5 | CONCLUSION

This study addresses the potential part mechanical ventilation and donor characteristics may play in the development of primary graft dysfunction in lung transplant patients. Despite the lower tidal volumes (lung protective ventilation), there was a high incidence of severe PGD. Thus, other variables may play an important role in the development of PGD. Both mechanical ventilation and other variables, such as lung ischemic time and the use of extracorporeal circulation should be further investigated to determine the primary inciting factors of PGD. Donor characteristics, for example, had a bearing on outcome compared to the recipient demographics in this study. By incorporating information gained on the role of donor characteristics and the importance of mechanical ventilations, the postoperative goal of lowering rates of primary graft dysfunction could be attained.

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CONFLICT OF INTEREST

To the best of our knowledge, there are no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTION

MM, RI, SH, AN, and SL participated in the design of the study. SL wrote the application for the ethical approval. SQ, AN, and SH collected the data. AN, MM, RI, SH, and SL analyzed the data. AN, SQ, and SL drafted the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Young KA, Dilling DF. The future of lung transplantation. Chest. 2019;155(3):465-473.
2. Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant. 2020;25(3):268-273.
3. Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT Working Group on primary lung graft dysfunction, part I: definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36(10):1097-1103.
4. Suzuki Y, Cantu E, Christie JD. Primary graft dysfunction. Semin Respir Crit Care Med. 2013;34(3):305-319.
5. Christie JD, Kotloff RM, Ahya VN, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med. 2005;171(11):1312-1316.
6. Daud SA, Yusen RD, Meyers BF, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2007;175(5):507-513.
7. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant. 2008;8(11):2454-2462.
8. Royer P-J, Olivera-Botello G, Koutskera A, et al. Chronic lung allograft dysfunction: a systematic review of mechanisms. Transplantation. 2016;100(9):1803-1814.
9. Whitson BA, Nath DS, Johnson AC, et al. Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg. 2006;131(1):73-80.
10. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis. 1988;137(5):1159-1164.
11. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369(22):2126-2136.
12. Leong R, Marks JA, Cereda M. How does mechanical ventilation damage lungs? What can be done to prevent it? In: Deutschman CS, Neligan PJ, eds. Evidence-Based Practice of Critical Care. Elsevier; 2020:642.
13. Lee JC, Christie JD. Primary graft dysfunction. Clin Chest Med. 2011;32(2):279-293.
14. Force ADT, RanieriVM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533.
15. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-1308.
16. Janz DR, Ware LB. Approach to the patient with the acute respiratory distress syndrome. Clin Chest Med. 2014;35(4):685-696.
17. Dezube R, Amaoutakis GJ, Reed RM, et al. The effect of lung-size mismatch on mechanical ventilation tidal volumes after bilateral lung transplantation. Interact Cardiovasc Thorac Surg. 2013;16(3):275-281.
18. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med. 2005;31(7):922-926.

19. Beer A, Reed RM, Böllükbas S, et al. Mechanical ventilation after lung transplantation. An international survey of practices and preferences. Ann Am Thorac Soc. 2014;11(4):546-553.

20. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25(7):745-755.

21. Lucangelo U, Del Sorbo L, Boffini M, Ranieri VM. Protective ventilation for lung transplantation. Curr Opin Anaesthesiol. 2012;25(2):170-174.

22. Eberlein M, Reed RM, Bolukbas S, et al. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. J Heart Lung Transplant. 2015;34(2):233-240.

23. Chambers DC, Cherikh WS, Harhay MO, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: donor and recipient size match. J Heart Lung Transplant. 2019;38(10):1042-1055.

24. Delom F, Danner-Boucher I, Dromer C, et al. Impact of donor-to-recipient weight ratio on survival after bilateral lung transplantation. Transplant Proc. 2014;46(5):1517-1522.

25. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single-lung transplantation is associated with allograft function and bronchiolitis obliterans syndrome. Chest. 2012;141(2):451-460.

26. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999;27(8):1492-1498.

27. Determann RM, Royakkers A, Woltluisz EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010;14(1):R1.

28. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective ventilation strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010;304(23):2620-2627.

29. Brower RG, Lanken PN, Macintyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351(4):327-336.

30. Shennib H, Massard G. Airway complications in lung transplantation. Ann Thorac Surg. 1994;57(2):506-511.

31. Verbeek GL, Myles PS, Westall GP, et al. Intra-operative protective mechanical ventilation in lung transplantation: a randomised, controlled trial. Anaesthesia. 2017;72(8):993-1004.

32. Futier E, Constantin J-M, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369(5):428-437.

33. Tugrul M, Camci E, Karadeniz H, Senturk M, Pembecki K, Akpir K. Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia. Br J Anaesth. 1997;79(3):306-310.

34. Unzueta MC, Casas JI, Moral MV. Pressure-controlled versus volume-controlled ventilation during one-lung ventilation for thoracic surgery. Anesth Analg. 2007;104(5):1029-1033.

35. Roze H, Lafargue M, Batoz H, et al. Pressure-controlled ventilation and intrabronchial pressure during one-lung ventilation. Br J Anaesth. 2010;105(3):377-381.

36. Wrigge H, Uhlig U, Zinserling J, et al. The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesthesia Analgesia. 2004;98(3):775-781.

37. Choi G, Wolthuis E, Bresser P, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology. 2006;105(4):689-695.

38. Unzueta C, Tusman G, Suarez-Sipmann F, Bohm S, Moral V. Alveolar recruitment improves ventilation during thoracic surgery: a randomized controlled trial. Br J Anaesth. 2012;108(3):517-524.

39. Roze H, Lafargue M, Perez P, et al. Reducing tidal volume and increasing positive end-expiratory pressure with constant plateau pressure during one-lung ventilation: effect on oxygenation. Br J Anaesth. 2012;108(6):1022-1027.

40. Maslow AD, Stafford TS, Davignon KR, Ng T. A randomized comparison of different ventilator strategies during thoracotomy for pulmonary resection. J Thorac Cardiovasc Surg. 2013;146(1):38-44.

41. Gu WJ, Wang F, Liu JC. Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials. CMAJ. 2015;187(3):E101-E109.

42. Qutub H, El-Tahan MR, Mowafi HA, El Ghoneimy YF, Regal MA, Al Safian AA. Effect of tidal volume on extravascular lung water content during one-lung ventilation for video-assisted thoracoscopic surgery: a randomised, controlled trial. Eur J Anaesthesiol. 2014;31(9):466-473.

43. Currey J, Pilcher DV, Davies A, et al. Implementation of a management guideline aimed at minimizing the severity of primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg. 2010;139(1):154-161.

44. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med. 2013;187(5):527-534.

45. Eberlein M, Arnaoutakis GJ, Yarmus L, et al. The effect of lung size mismatch on complications and resource utilization after bilateral lung transplantation. J Heart Lung Transplant. 2012;31(5):492-500.

46. Eberlein M, Diehl E, Bolukbas S, Merlo CA, Reed RM. An oversized allograft is associated with improved survival after lung transplantation for idiopathic pulmonary arterial hypertension. J Heart Lung Transplant. 2013;32(12):1172-1178.

47. Thakuria L, Davey R, Romano R, et al. Mechanical ventilation after lung transplantation. J Crit Care. 2016;31(1):110-118.

48. Benazzo A, Schwarz W, Frommlet F, et al. Donor ventilation parameters as predictors for length of mechanical ventilation after lung transplantation: results of a prospective multicenter study. J Heart Lung Transplant. 2021;40(1):33-41.

49. Verbeek GL, Myles PS. Intraoperative protective ventilation strategies in lung transplantation. Transplant Rev (Orlando). 2013;27(1):30-35.

50. Bansal R, Esan A, Hess D, et al. Mechanical ventilatory support in potential lung donor patients. Chest. 2014;146(1):220-227.

51. Diamond JM, Ahya VN. Mechanical ventilation after lung transplantation. It’s time for a trial. Ann Am Thorac Soc. 2014;11(4):598-599.

52. Barnes L, Reed RM, Parekh KR, et al. Mechanical ventilation for the lung transplant recipient. Curr Pulmonol Rep. 2015;4(2):88-96.

53. Geube M, Anandamurthy B, Yared JP. Perioperative management of the lung graft following lung transplantation. Crit Care Clin. 2019;35(1):27-43.

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