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Lung protective ventilation guided by driving pressure improves pulmonary outcomes in heart transplantation

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This study aimed to investigate whether driving pressure-guided ventilation can reduce postoperative pulmonary complications in patients who have undergone heart transplantation. Patients who underwent orthotopic heart transplantation were divided into two groups according to the perioperative ventilation strategy: (1) conventional lung-protective ventilation (group C) and (2) driving pressure-guided ventilation (group D). The primary outcome was the occurrence of postoperative pulmonary complications within 30 days of surgery. Univariate and multivariate logistic regression analyses were performed to evaluate the independent risk factors associated with postoperative pulmonary complications (PPCs). Compared with group C, patients in group D exhibited lower driving pressure. Oxygenation improved significantly in the early period after surgery in patients in group D. Group C exhibited a higher number of patients with postoperative pulmonary complications, especially respiratory infections and atelectasis. Patients in group D experienced a shorter duration of postoperative mechanical ventilation and a shorter stay in the intensive care unit. The conventional ventilation strategy, the high driving pressure level and the low PaO2 value at the end of the surgery were the independent risk factors for PPCs in heart transplantation. Compared with conventional lung-protective ventilation, driving pressure-guided ventilation was associated with improved pulmonary oxygenation and lower incidences of pulmonary complications among patients after heart transplantation.

Keywords Driving pressure, Lung protective ventilation, Heart transplantation, Postoperative pulmonary complications

Postoperative pulmonary complications (PPCs) are a spectrum of new-onset respiratory adverse events occurring within 5 to 7 days after surgery[1,2]. These complications contribute to a 30-day mortality of 20–44% after cardiac surgery[3–6]. Driving pressure (ΔP), defined as the difference between plateau airway pressure and positive end-expiratory pressure (PEEP), was first introduced by Amato et al. in 2015 in their meta-analysis study on acute respiratory distress syndrome[7]. This parameter was most strongly associated with survival among various ventilation parameters. A lower ΔP has been verified to be closely relative to an ameliorative prognosis after surgery[8,9]. However, controversy persists regarding whether ΔP-guided ventilation can decrease the incidence of PPCs[10–12].

In patients with end-stage heart failure, persistent positive intrathoracic pressure has the potential to reduce venous return and increase pulmonary vascular resistance, leading to hypotension. Consequently, implementing the PEEP setting, a crucial ventilation parameter in ΔP-guided ventilation, may be challenging. In addition, elevation of the right ventricular afterload due to hypopnea-induced hypercapnia poses significant challenges to anesthesiologists during perioperative hemodynamic management.

Given the need for additional evidence to confirm the relationship between ΔP and PPCs, this study aimed to assess the efficacy and safety of the ΔP-guided ventilation strategy in preventing PPCs in heart transplantation.

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Methods

Consecutive patients with end-stage heart failure who underwent orthotopic heart transplantation at our center were included in this prospective observational cohort study. The exclusion criteria were: (1) being younger than 18 years; (2) sepsis within twelve weeks of surgery; (3) obstructive sleep apnoea syndrome requiring long-term ventilation assistance; (4) advanced-stage myasthenia gravis; (5) a body mass index > 30 kg·m-2; (6) reluctance to participate in the study; (7) mortality during surgery; (8) alteration of the initial ventilation strategy during surgery for reasons such as refractory hypoxemia (arterial oxygen saturation < 88% despite 100% oxygen inhalation), interference with the surgical field exposure, intolerable hypercapnia, or ventilation-related hemodynamic instability; and (9) attainment of the expected sample size. All the enrolled patients were divided into two groups at a 1:1 ratio according to the intraoperative ventilation strategy employed, with group C receiving conventional lung-protective ventilation and group D receiving driving pressure-guided ventilation. All clinical data, including baseline characteristics, intraoperative ventilation parameters, surgical information, incidence of PPCs, incidence of postoperative adverse cardiovascular events and all-cause death, length of stay in the intensive care unit (LOS-ICU), ventilation assistance time, and incidences of postoperative extrapulmonary complications were collected via the Hospital Information System and Anesthesia Information Management System. Definitions of the perioperative variables are provided in the Supplementary Data.

All patients received a standardized general anesthesia from anesthesiologists with at least 10 years of experience in cardiovascular anesthesia. A continuous pulse oximeter (BSA09001P, Berry Electronic Technology, China) measured SpO2. Catheterization was routinely performed in the peripheral, central venous, and pulmonary arteries for invasive hemodynamic monitoring (Vigilance Cell; Edwards Lifesciences Corporation, USA). The core body temperature of each patient was monitored with a nasopharyngeal detector (MR411, Mindray Biomedical Electronics Co., Ltd., Germany). Myocardial ischemia and malignant arrhythmia were routinely monitored using a 12-lead electrocardiogram. Transesophageal echocardiography (EPIQ 7 C; Philips Ultrasound, Inc., USA) was performed on all patients to evaluate their cardiac function and volume status. During the induction period, the dosages of sufentanil, etomidate, and rocuronium were 1.5 to 2.5 μg·kg-1, 0.2 to 0.6 mg·kg-1 and 0.6 to 1.2 mg·kg-1 respectively and dexmedetomidine (0.2 to 0.4 μg·kg-1·h-1), sufentanil (1.0 to 1.5 μg/kg intermittent injection), rocuronium (0.3 to 0.6 mg·kg-1·h-1) and propofol (2.0 to 4.0 mg·kg-1·h-1) were regularly administered for anaesthetic maintenance.

The application of inotropic and vasoactive agents was initiated after rewarming, with the recommended dosage regimens being as follows: dopamine 3.0 to 5.0 μg·kg-1·min-1, dobutamine 3.0 to 5.0 μg·kg-1·min-1, epinephrine 0.04 to 0.1 μg·kg-1·min-1, milrinone 0.4 to 1.0 μg·kg-1·min-1, treprostinil 0.625 to 1.25 ng·kg-1·min-1, and nitric oxide inhaled at a concentration of 15 to 30 ppm.

A similar mechanical ventilation mode and target were used in all patients until extubation (ZEUS IE; Draeger Medical Systems, Inc., USA) (Table 1). There were two different PEEP setting rules in our center, plan A was the lowest driving pressure: a 10-cycle experimental ventilation was carried out at each level of PEEP after intubation, and the ΔP of the last cycle was recorded. The PEEP value corresponding to the lowest ΔP was recognized as the optimal ventilation parameter. This parameter was subject to modification upon cessation of ventilation, ICU admission, and every morning throughout the ventilation period. Plan B was to maintain PEEP at the level facilitating optimal oxygenation during the off-pump period. The cardiovascular anesthesiologists chose the PEEP setting plans freely, and the patients receiving plan A were classified into group D, and those receiving plan B were enrolled into group C. Both of the ventilation strategies were acceptable to all of the adult patients in our center and were performed by anesthesiologists according to their specialities and preferences.

The times for the alveolar recruitment maneuvers were as follows: (1) after intubation; (2) at any time after the ventilation pause; (3) before cardiopulmonary bypass withdrawal; (4) before sternal closure; and (5) when hypoxemia occurred for > 10 s. Partial pressure of carbon dioxide (PaCO2) monitoring was employed to determine the tidal volume and respiratory rate. Inspiration/expiration pattern was adjusted based on the

Initial ventilation parameters	Plan A	Plan B
Mode	Pressure regulated volume control	
Tidal volume - mL	6 mL/Kg PBW* (not exceed 8mL/Kg PBW)	6 mL/Kg PBW* (not exceed 8mL/Kg PBW)
Respiratory rate - cycle per minute	10	10
Inspiratory/expiratory ratio	1:1.5**	
Inspiratory oxygen fraction - %	50	
PEEP setting rules	Lowest driving pressure (not exceed 8 cm H_2O)	Optimal oxygenation function (not exceed 8 cm H_2O)
On-pump Ventilation	Tidal volume: 4 mL/Kg PBW Respiratory rate: 4 circle per minute Positive end-expiratory pressure: 4 cm H_2O Inspiratory oxygen fraction: 21%	
Ventilatory target	(1) $SpO_2 \geq 90\%$ or $PaO_2 \geq 60$ mm Hg; (2) $PaCO_2$: 35 ~ 50 mm Hg and (3) pH value > 7.20	

Table 1. Ventilation strategy. * PBW (Kg) = [50 (male) or 45.5 (female) + 0.91×(height in centimeter - 152.4)] Kg; **1:2.5 - 1:3 in the patients with chronic obstructive pulmonary disease; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SpO_2: peripheric arterial oxygen saturation.

preoperative small airway condition. During cardiopulmonary bypass surgery, mechanical ventilation was maintained using the low-level parameters described in Table 1.

Intraoperative ventilation parameters, including ΔP (cm H2O) (plateau airway pressure minus PEEP), PEEP (cm H2O), tidal volume (mL), dynamic respiratory system compliance (CRS) (calculated as the tidal volume (mL)/ΔP (cm H2O), mL/cm H2O)[13], SpO2 (%), and the end-tidal carbon dioxide (mm Hg), were measured at two time points: 15 min after intubation and the end of the operation.

Management of hypoxemia (supplementary data) was initiated immediately through the following steps: (1) carefully checking anesthesia apparatus malfunction, airway normality, and monitoring accuracy; (2) improving cardiac function, correcting fluid overload, and alleviating systemic inflammation; (3) performing alveolar recruitment maneuvers as described above; (4) increasing the tidal volume and PEEP within the upper limits, which were introduced in Table 1; (5) increasing the respiratory rate while addressing concurrent hypercapnia; (6) titrating the fraction of inspiratory oxygen until the SpO2 reaches or exceeds 90%; and (7) considering the use of extracorporeal membrane oxygenation if any following situations occurred[14]: (a) a PaO2/FiO2 < 50 mm Hg for more than 3 h; (b) a PaO2/FiO2 of < 80 mm Hg for more than 6 h; or (c) a critical respiratory acidosis (pH < 7.25 and PaCO2 ≥ 60 mm Hg) for more than 6 h.

The primary outcome was the occurrence of new-onset PPCs within 30 days of surgery. PPCs were defined as any postoperative respiratory system complication that occurred from admission to the ICU to 30 days post-surgery, encompassing (1) respiratory infection, (2) respiratory failure, (3) bronchospasm, (4) atelectasis, (5) pleural effusion, (6) pneumothorax, and (7) aspiration pneumonitis, as delineated in previously published literature[15].

Secondary outcomes included the perioperative PaO2/FiO2, early/late death, vasoactive-inotropic score at the end of surgery, postoperative adverse cardiovascular events, LOS-ICU, ventilation assistance time, and postoperative extrapulmonary complications. GEM Premier 3500 (Wolfen Scientific, Inc., USA) was applied for arterial blood gas analyses, with the time points: T1 (before surgery), T2 (after intubation), T3 (withdrawal from cardiopulmonary bypass), T4 (end of surgery), T5 (postoperative day 1), T6 (postoperative day 3), T7 (postoperative day 5), and T8 (postoperative day 7). The average values of multiple blood gas measurements were used for statistical analysis. A systolic pressure < 80% of baseline or a mean blood pressure < 65 mmHg during ventilation was recognized as ventilation-related hypotension, excluding other risk factors for hemodynamic instability, such as low cardiac output syndrome, surgical procedures, anaphylaxis, pharmacological action, or massive hemorrhage. The vasoactive-inotropic score is the sum of the dosages of frequently used vasoactive or inotropic agents according to their weighted values[16]. The postoperative adverse cardiovascular events included new-onset lethal arrhythmias (supraventricular/ventricular tachycardia, ventricular fibrillation, or Adams-Stokes syndrome), acute myocardial infarction, cardiogenic shock, and thrombotic or embolic events. Early death was defined as any death occurring within 7 days of surgery, while late death was considered for deaths occurring within 30 days after the surgery was scheduled. Postoperative extrapulmonary complications included tracheotomy, rethoracotomy for exploration, wound infection, sepsis, gastrointestinal hemorrhage, and neurological complications (such as delayed recovery, delirium, cognitive dysfunction, coma, new-onset stroke, and syncope).

SPSS 25.0 (SPSS, Inc., USA), GraphPad Prism 8.0 (GraphPad Software, USA), and PASS 15.0 (NCSS, LLC, USA) were utilized in statistical analyses. Categorical variables, such as the baseline characteristics in each study group, were presented as proportions and were compared using the chi-square test or Fisher's exact test. Continuous variables were presented as means ± standard deviations (normal distribution) or medians and interquartile ranges (abnormal distribution). They were compared using the Student's t-test (normal distribution) or Wilcoxon test (abnormal distribution). Repeated-measures analysis of variance was applied to assess the differences in the perioperative PaO2/FiO2 and PaCO2 between patients in the two groups. Univariate and multivariate logistic regression were performed in the risk factor analysis for PPCs. Previous studies revealed that the morbidities of PPCs in cardiac surgery were reduced to 55%[17]with the PLV strategy, and the incidence under conventional ventilation was as high as 88%[18]. We calculated that the study required a minimum of 44 cases in each group (two-sided α error level of $P < 0.05$, β error level = 0.1, dropout rate = 0.1). Enrolment was automatically stopped when the sample size reached 44 patients in each group. Statistically significant was defined as $P < 0.05$.

This prospective study followed the Declaration of Helsinki and was approved by the local ethics committee at Fujian Medical University Union Hospital (2022YF022-01), and all participants provided written informed consent. All organs were procured via Organ Procurement Organizations in Fujian medical university union hospital. All methods were performed in accordance with the relevant guidelines and regulations.

Results

Between March 2019 and March 2023, 98 consecutive patients who underwent orthotopic heart transplantation at our center were screened for this study. The following cases were excluded: six patients were automatically excluded as enrolment reached the expected sample size for group D, two patients were younger than 18 years old, one patient experienced severe hypotension during the alveolar recruitment maneuver, and one patient underwent veno-arterial extracorporeal membrane oxygenation in the operating room due to hyperacute rejection and low cardiac output syndrome received protective ventilation according to a published reference (tidal volume: 4 mL·kg-1 predicted body weight, PEEP: 10 cm H2O, fraction of inspiratory oxygen: 0.3, respiratory rate: 4 cycles per minute)[19]. Finally, 88 patients were enrolled in this study and followed up for 30 days after surgery (Fig. 1). No deaths occurred during surgery. There were no statistical distinctions in any of the perioperative baseline characteristics between the patients of the two groups (Table 2).

The intraoperative mechanical ventilation parameters of all the objects are described in Table 3. Repeated-measures analysis of variance indicated a prominent difference in the perioperative PaO2/FiO2 between the

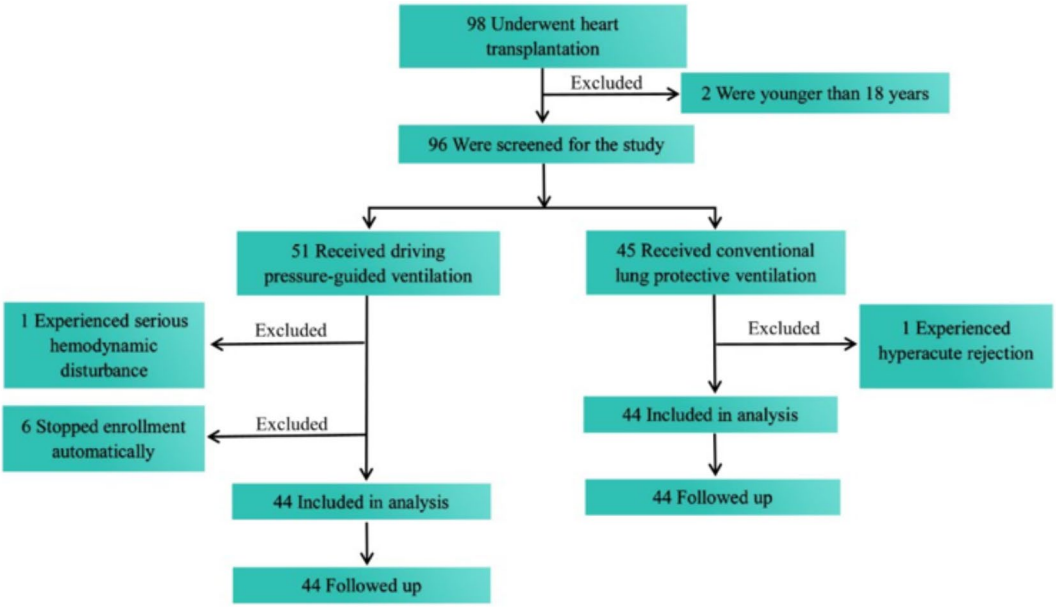

Fig. 1. Flow chart of the study inclusion. Between March 2019 and March 2023, 98 patients underwent orthotopic heart transplantation at our center, and 96 patients were screened for study inclusion. Eight patients who met the exclusion criteria were excluded from this study: six cases were automatically excluded as enrolment reached the expected sample size for group D, two cases were younger than 18 years, one case had severe hypotension due to alveolar recruitment maneuver, and one case had hyperacute rejection with intraoperative veno-arterial extracorporeal membrane oxygenation assistance. Finally, an observational study of 88 patients was conducted over a 30-day follow-up period.

two groups ($F=4.204$, $P<0.001$). Sidak's multiple comparisons test found that the PaO2/FiO2 of the patients in Group D were notably higher than those in Group C at T3 (326.1 ± 35.4 vs. 291.2 ± 56.7, $t=3.869$, $P=0.001$), T4 (339.4 ± 42.0 vs. 301.3 ± 38.1, $t=4.223$, $P<0.001$) and T5 (357.8 ± 37.4 vs. 327.2 ± 45.5, $t=3.392$, $P=0.006$). However, no significant differences were discovered at other time points. In addition, no significant differences were observed between the two patient groups regarding the PaCO2 levels ($F=1.370$, $P=0.215$) (Fig. 2).

The differences in the morbidities of PPCs, postoperative adverse cardiovascular events, all-cause death, and other complications are shown in Table 4; Fig. 3. In group D, one patient died of cardiogenic shock on postoperative day 2, and no early death was observed in group C. In total, five late deaths (5/88, 5.7%) were observed, including one case of cardiogenic shock, one case of sepsis in group D, two cases of multiple organ failure, and one case of sepsis in group C (Table 4). Four patients (4/88, 4.5%) experienced adverse cardiovascular events after surgery. In group D, despite receiving veno-arterial extracorporeal membrane oxygenation, two patients died from cardiogenic shock on postoperative days 2 and 9. In addition, one patient with deep venous thrombosis in the lower limb recovered after anticoagulant therapy. In group C, one case of severe right heart failure was observed, which recovered after seven days of venoarterial extracorporeal membrane oxygenation assistance.

Following the univariate analysis, the multivariate logistic regression analysis covered four variables. Finally, the conventional ventilation strategy, the high ΔP level (after intubation, at the end of the surgery), and the low PaO2 value (at the end of the surgery) were identified as independent risk factors for PPCs in heart transplantation (Table 5).

Discussion

Orthotopic heart transplantation remains a standard surgical strategy for patients with end-stage heart failure[20]. No severe or persistent hypotension requiring inotropic support was observed in patients in this study, indicating that the low- to moderate-level of PEEP and alveolar recruitment maneuvers were well tolerated during heart transplantation. In our study, patients in group D exhibited higher PaO2/FiO2 in the early postoperative stages, leading to earlier intubation and a shorter LOS-ICU than patients in group C. This suggests that ΔP-guided ventilation has an advantage in promoting the recovery of postoperative pulmonary oxygenation. This could also explain why inspiratory infection and atelectasis significantly decreased in patients in group D after surgery.

ΔP represents the magnitude of cyclic parenchymal deformation applied to ventilated, preserved lung units. It is considered the most accessible and easiest way to calculate cyclic lung strain, a predictor of lung injury that outperforms tidal volume. Further, dynamic respiratory system compliance quantifies functional lung size during disease better than predicted body weight 7. In this study, although the PEEP of patients in group D was higher than in group C, the ΔP-guided ventilation strategy did not significantly elevate airway pressure. We speculated that a more individualised PEEP level plays a role in maintaining the openness of alveoli during low tidal volume ventilation. This, in turn, leads to a notable increase in dynamic respiratory system compliance.

Category	Group D (*n*=44)	Group C (*n*=44)	t/χ^2	*P*
Age - y	49.2±6.4	51.2±7.3	1.367	0.175
Male - n (%)	27 (61.4)	29 (65.9)	0.196	0.658
Predicted body weight - Kg	59.3±11.2	61.2±8.9	0.881	0.381
Body mass index	22.4±2.1	22.8±1.9	0.937	0.351
Active smoking - n (%)	13 (29.6)	15 (34.1)	0.210	0.647
Underlying diseases - n (%)				
Chronic lung diseases	4 (9.1)	2 (4.6)	0.715	0.398
Respiratory infection	5 (11.4)	4 (9.1)	0.352	0.725
Cardiopulmonary resuscitation	1 (2.3)	1 (2.3)	<0.001	> 0.999
Hypertension	14 (31.8)	16 (36.4)	0.202	0.653
Diabetes Mellitus	3 (6.8)	6 (13.6)	1.114	0.291
Hyperlipidemia	5 (11.4)	5 (9.1)	<0.001	>0.999
Cerebrovascular diseases	2 (4.6)	1 (2.3)	0.588	0.557
Chronic kidney disease	2 (4.6)	1 (2.3)	0.588	0.557
Hypoxemia - n (%)	13 (29.6)	15 (34.1)	0.458	0.647
Left ventricular ejection fraction - %	18.4±9.3	20.6±8.5	1.158	0.250
ASA class 3 and above - n (%)	41 (93.2)	42 (95.5)	0.212	0.645
EuroSCORE II	9.1±3.5	9.7±4.1	0.738	0.462
NYHA class III and IV - n (%)	42 (95.5)	43 (97.7)	0.345	0.557
Lung injury prediction score	4.2±1.1	4.1±1.3	0.021	0.698
Pulmonary vascular resistance - wood	2.8±0.8	2.7±0.6	0.663	0.509
Donor informations				
Age - y	46.2±7.8	46.2±7.8	1.357	0.178
Male- n (%)	29 (65.9)	29 (65.9)	29 (65.9)	29 (65.9)
Weight - Kg	68.2±13.0	66.5±11.6	0.647	0.519
Heart ischemic time - h	3.7±1.5	3.9±1.3	0.668	0.506
Left ventricular ejection fraction - %	59.1±5.8	58.7±6.3	0.310	0.757
Postoperative mechanical assistance - n (%)				
Intra-aortic balloon pump	2 (4.6)	1 (2.3)	<0.001	> 0.999
Extracorporeal membrane oxygenation	3 (6.8)	1 (2.3)	1.048	0.306
Continual renal replacement therapy	2 (4.6)	2 (4.6)	<0.001	> 0.999
Surgical disease - n (%)				
Dilated cardiomyopathy	34 (77.3)	39 (88.6)	3.454	0.327
Hypertrophic cardiomyopathy	5 (11.4)	4 (9.1)		
Ischemic cardiomyopathy	3 (6.8)	1 (2.3)		
Valvular disease	2 (4.6)	0 (0.0)		
Surgery time - h	5.6±1.2	5.5±1.5	0.345	0.731
Cardiopulmonary bypass time - min	112.0±23.4	119.7±28.8	1.376	0.172
Aortic cross-clamping time - min	61.2±11.2	58.1±13.7	1.162	0.248
Intraoperative blood loss - mL	532.9±123.5	528.0±114.4	0.193	0.847
Intraoperative transfusion				
Suspension red blood cells - IU	0.6±0.5	0.7±0.8	0.703	0.484
Fresh frozen plasma - mL	171.2±52.5	159.7±69.1	0.879	0.382
Apheresis platelets - IU	1.1±0.6	1.3±0.5	1.699	0.093
Intraoperative infusion - mL	635.1±249.7	655.2±314.7	0.332	0.741
The categorical variables were presented as n (%), and the distributions variables were presented as mean ± standard deviation.				

Table 2. Baseline characters.

These results indicate that the ΔP might be a more suitable factor for guiding decision-making regarding the ventilation strategy employed during heart transplantation, which is in line with a previous study by Mathis and colleagues, who held the same opinion that ΔP, but not tidal volume or PEEP, was closely relative to reduced PPCs in heart surgery[16].

Perioperative ventilation strategies should focus on minimising any increase in the afterload of the right ventricle[21]. A low tidal volume ventilation strategy significantly affects the ΔP and is one of the most critical key points in protective lung ventilation. In addition to utilizing the ΔP, international experts advocate for a

Category	Group D (*n*=44)	Group C (*n*=44)	t	*P*
After induction				
Driving pressure - cm H_2O	12.5±2.4	14.2±3.7	2.557	0.012
Peak inspiratory pressure* - cm H_2O	18.3±2.6	17.4±2.5	1.665	0.102
Positive end-expiratory airway pressure - cm H_2O	4.8±1.5	4.1±1.2	2.072	0.018
Tidal volume - mL	432.7±35.4	445.8±43.0	1.560	0.122
Respiratory rate - cycle per minute	11.4±1.6	11.9±1.3	1.609	0.111
Dynamic respiratory system compliance - mL/cm H_2O	36.3±7.9	31.2±8.6	2.329	0.005
SpO_2 - %	98.5±0.8	98.3±0.7	1.248	0.215
End-tidal carbon dioxide - mm Hg	39.5±3.1	38.8±3.4	1.009	0.316
At the end of surgery				
Driving pressure - cm H_2O	12.9±2.6	15.2±3.5	3.499	<0.001
Peak inspiratory pressure* - cm H_2O	18.5±2.8	19.3±2.5	1.414	0.161
Positive end-expiratory airway pressure - cm H_2O	5.1±1.7	4.6±1.5	1.463	0.147
Tidal volume - mL	441.6±38.9	468.4±45.2	2.981	0.004
Respiratory rate - cycle per minute	11.5±1.1	11.7±0.9	0.933	0.353
Dynamic respiratory system compliance - mL/cm H_2O	33.9±6.7	30.5±7.5	2.243	0.028
SpO_2 - %	97.3±1.0	96.5±1.2	3.397	0.001
End-tidal carbon dioxide - mm Hg	38.6±4.6	37.2±3.7	1.573	0.119

Table 3. Intraoperative mechanical ventilation parameters. The categorical variables were presented as n (%), and the distributions variables were presented as mean ± standard deviation. * Peak inspiratory pressure equated to the plateau pressure in pressure regulated volume control mode.

low tidal volume ranging from 4 to 8 mL·kg-1 predicted body weight during surgery[22]. A previous prospective cohort study of 9359 patients revealed that a tidal volume of 6 mL·kg-1 improved postoperative oxygenation and in-hospital survival after cardiac surgery[23]. We hypothesized that the positive results were attributed to the combination of low ΔP accompanied by low tidal volume despite maintaining a relatively higher PEEP level than the conventional lung-protective ventilation strategy. However, hypoxemia and hypercapnia generated by hypoventilation cannot be neglected during heart transplantation, as they increase the risk of pulmonary arterial hypertension during surgery. Therefore, we modified the upper limit of PaCO2 to 50 mmHg (mild hypercapnia)[24] during the ventilatory period. In addition, less postoperative atelectasis was observed in group D, and a similar frequency of ventilation-related hemodynamic disturbances and probability of postoperative adverse cardiovascular events was observed. The same was true for serious hypercapnia, which was evaluated using PaCO2 measurements derived from blood gas analyses and end-tidal carbon dioxide monitoring. Overall, the perioperative application of the low-tidal volume ventilation appeared safe for heart transplantation.

Currently, maintaining ventilation during extracorporeal circulation remains debatable. A meta-analysis involved 748 patients who underwent cardiac surgery (15 clinical trials) and suggested that continuous positive airway pressure ameliorated the postoperative alveolar-arterial oxygen gradient difference. However, continuous positive airway pressure or maintaining ventilation during extracorporeal circulation did not improve the prognosis in low- or moderate-risk patients undergoing selective heart surgery, and the evidence was inconclusive due to heterogeneity and small sample size[25]. In contrast, the PROVECS study enrolled 488 randomized patients who underwent on-pump cardiac surgery and revealed that ventilation during cardiopulmonary bypass did not reduce the incidence of PPCs compared with routine standard care. It supported the idea that patients undergoing on-pump cardiac surgery did not benefit from ventilation during the on-pump period 16. It is worth noting that intermittent inflation of the lung during cardiopulmonary bypass makes it difficult to expose the surgical field. Although low-setting ventilation during the cardiopulmonary bypass period has been habitually applied in our center, few high-quality studies have proven the relationship between on-pump period ventilation and a reduction in PPCs during cardiac surgery[26,27].

This study was not without limitations. First, as a single-center prospective observational study, we could not represent the capacities of other medical institutions in the perioperative management of heart transplantation. Second, despite no significant difference in the patient baseline between the two groups, the selection bias could not be fully eliminated which originated from the anesthesiologists' choice of intraoperative ventilation strategies. Randomized clinical trials are required to support the authors' conclusion. Third, there were five authorized surgical teams for heart transplantation, leading to heterogeneity in perioperative management and prognosis. Forth, due to emergency operations, there were frequent instances of incomplete preoperative pulmonary function examinations, resulting in an inaccurate evaluation of perioperative status and the potential for unbalanced baseline risks.

Conclusions

Compared with conventional lung-protective ventilation, the ΔP-guided ventilation strategy enhanced oxygenation in the early period after surgery. It exhibited a strong correlation with a reduced incidence of

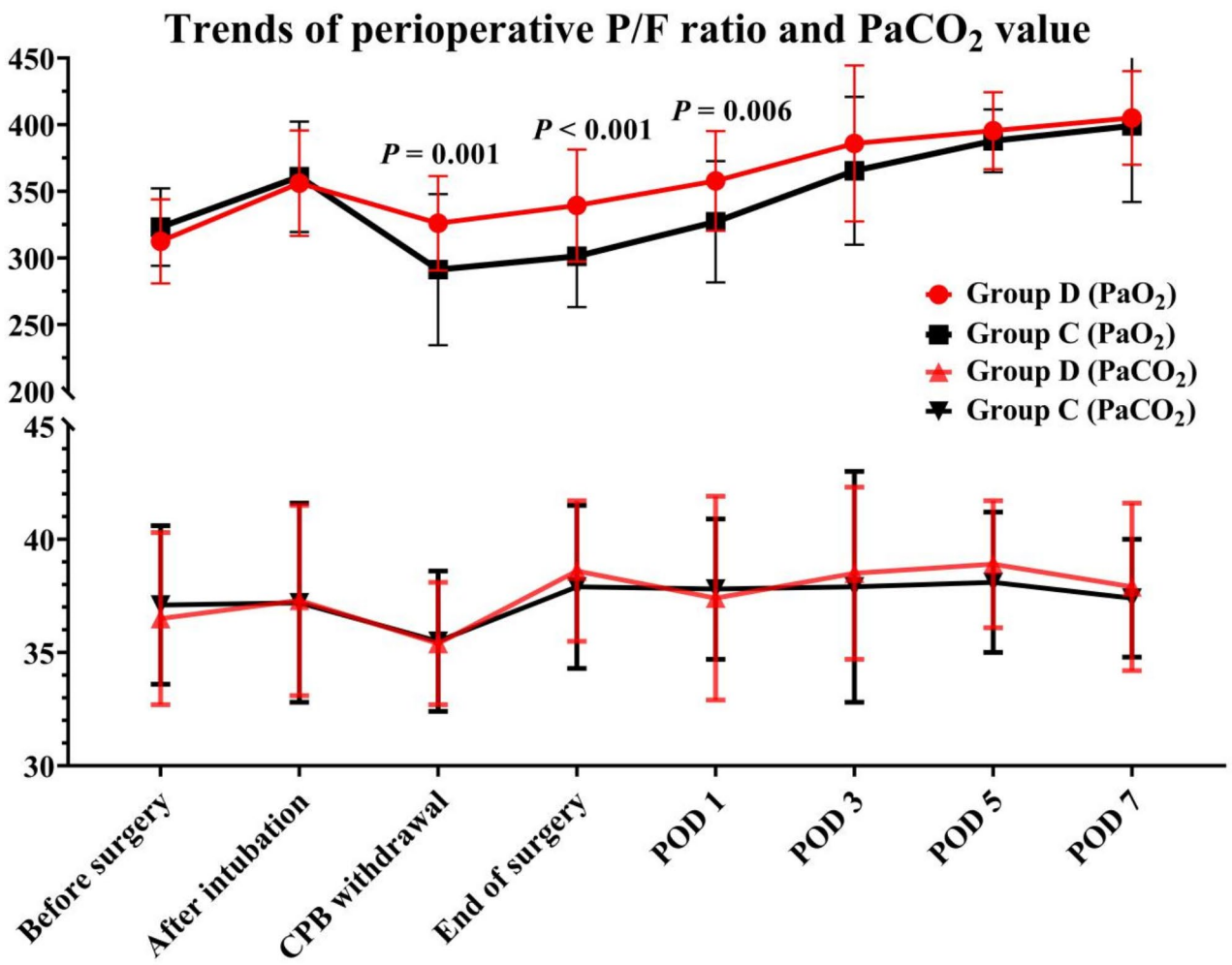

Fig. 2. Trends of perioperative PaO2/FiO2 and PaCO2 values. CPB, cardiopulmonary bypass; POD, postoperative day.

PPCs, a shorter duration of postoperative ventilation, and a shorter LOS-ICU after heart transplantation. ΔP and SpO2 at the end of surgery are independent risk factors for PPCs. There was no evidence that this novel ventilation strategy had more obvious hemodynamic disturbances or interference with surgical procedures than conventional lung-protective ventilation during heart transplantation.

Statements & Declarations.

Category	Group D (*n*=44)	Group C (*n*=44)	RR (95%CI)	t/χ^2	*P*
Primary outcomes					
Any PPCs - n (%)	13 (36.1)	23 (63.9)	0.61 (0.36–0.96)	4.701	0.030
Respiratory infection	6 (13.6)	16 (36.4)	0.47 (0.22–0.88)	6.061	0.014
Respiratory failure	1 (2.3)	3 (6.8)	0.49 (0.09–1.43)	1.048	0.306
Bronchospasm	1 (2.3)	2 (4.6)	0.66 (0.12–1.65)	< 0.001	> 0.999
Atelectasis	9 (20.5)	18 (40.9)	0.58 (0.31–0.97)	4.328	0.038
Pleural effusion	5 (11.4)	6 (13.6)	0.90 (0.41–1.54)	< 0.001	> 0.999
Pneumothorax	0 (0.0)	0 (0.0)	/	/	/
Aspiration pneumonitis	1(2.3)	0 (0.0)	2.02 (0.41–20.02)	1.011	0.315
Secondary outcomes					
Early death* - n (%)	1 (2.3)	0 (0.0)	2.02 (0.41–20.0)	< 0.001	> 0.999
Late death** - n (%)	2 (4.6)	3 (6.8)	0.79 (0.23–1.62)	< 0.001	> 0.999
Ventilation-related hypotension - n	3.9±1.3	3.6±1.2	/	1.125	0.264
Vasoactive-inotropic score at the end of surgery	26.1±3.8	26.5±4.5	/	0.021	0.985
Postoperative cardiovascular adverse events - n (%)	3 (6.8)	1 (2.3)	1.537 (0.60–2.24)	0.262	0.609
Length of stay in ICU - d	4.6±6.2	7.8±7.8	/	2.130	0.036
Duration of ventilation - d	2.2±5.1	4.9±6.3	/	2.210	0.030
Tracheotomy - n (%)	1 (2.3)	2 (4.6)	0.66 (0.12–1.65)	< 0.001	> 0.999
Rethoracotomy for exploration - n (%)	1 (2.3)	0 (0.0)	2.02 (0.41–20.0)	< 0.001	> 0.999
Wound infection - n (%)	1 (2.3)	2 (4.6)	0.66 (0.12–1.65)	< 0.001	> 0.999
Sepsis - n (%)	2 (4.6)	4 (9.1)	0.65 (0.19–1.44)	0.715	0.398
Gastrointestinal hemorrhage - n (%)	1 (2.3)	1 (2.3)	1.00 (0.19–1.96)	0.512	0.474
Neurological complications - n (%)	3 (6.8)	5 (11.4)	0.73 (0.26–1.44)	0.550	0.458
Mechanical assistance - n (%)					
Intra-aortic balloon pump	3 (6.8)	2 (4.6)	1.22 (0.46–1.97)	< 0.001	> 0.999
Extracorporeal membrane oxygenation	2 (4.6)	1 (2.3)	1.35 (0.41–2.12)	< 0.001	> 0.999
Continual renal replacement therapy	4 (4.6)	5 (5.7)	0.88(0.36–1.56)	0.124	0.725

The categorical variables were presented as n (%), and the distributions variables were presented as mean ± standard deviation. * death within 7 days after surgery; ** death within 30 days after surgery. PPCs: postoperative pulmonary complications.

Table 4. Outcomes.

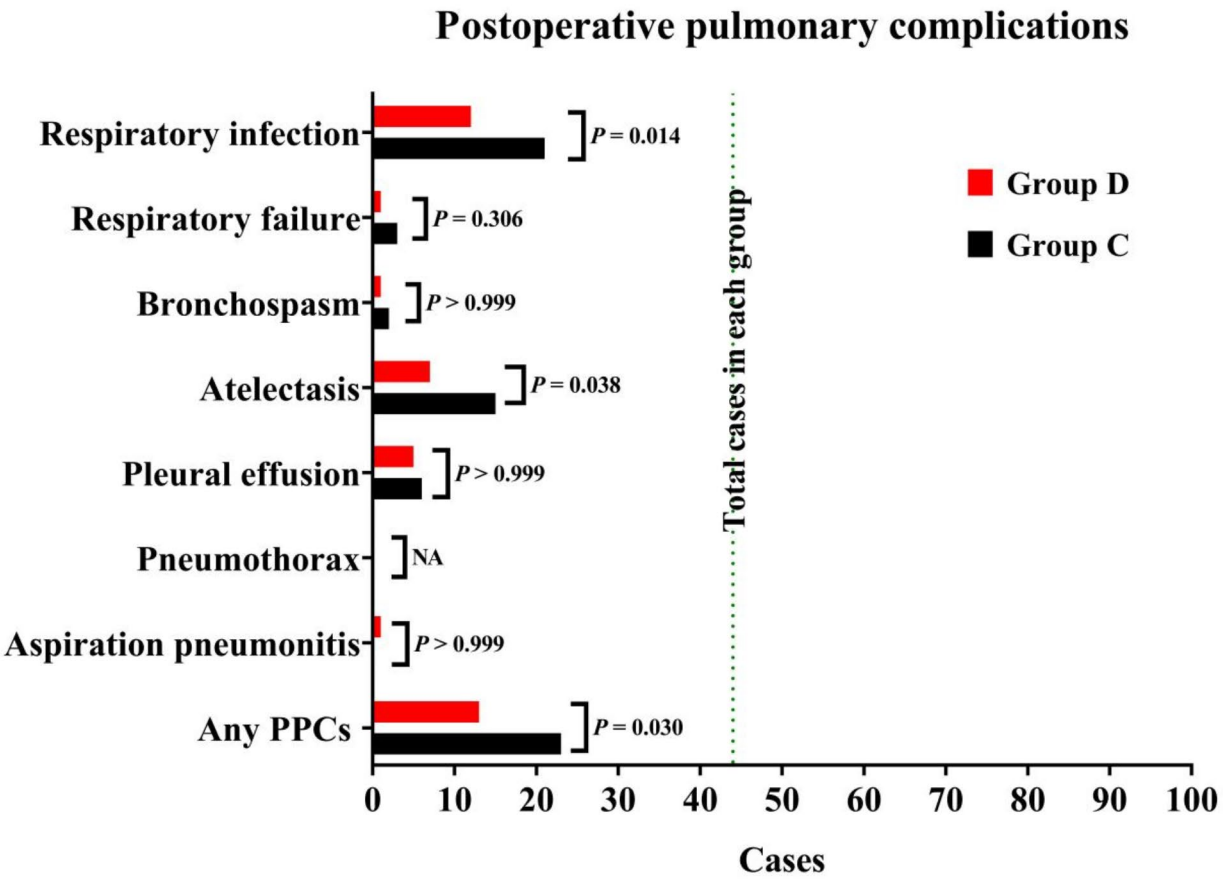

Fig. 3. Proportions of postoperative pulmonary complications. The histogram shows the incidence of all types of PPCs, as defined in the Methods section. PPCs: Postoperative pulmonary complications.

Variables	Univariate					Multiriate				
	β	S.E	Z	*P*	OR (95%CI)	β	S.E	Z	*P*	OR (95%CI)
Group*	−0.96	0.45	−2.15	0.032	0.38(0.16 ~ 0.92)	−0.51	0.64	−2.80	0.026	0.66(0.48 ~ 0.86)
After induction										
Driving pressure	0.19	0.08	2.49	0.013	1.21(1.04 ~ 1.41)	0.25	0.10	2.58	0.010	1.29(1.06 ~ 1.56)
Peak inspiratory pressure	0.06	0.09	0.66	0.511	1.06(0.89 ~ 1.25)	/	/	/	/	/
Positive end-expiratory airway pressure	−0.14	0.16	−0.88	0.377	0.87(0.64 ~ 1.18)	/	/	/	/	/
Tidal volume	−0.01	0.01	−0.92	0.355	0.99(0.98 ~ 1.01)	/	/	/	/	/
Respiratory rate	0.16	0.14	1.16	0.247	1.18(0.89 ~ 1.55)	/	/	/	/	/
Dynamic respiratory system compliance	0.01	0.03	0.52	0.604	1.01(0.96 ~ 1.07)	/	/	/	/	/
SpO_2	0.21	0.28	0.74	0.458	1.23(0.71 ~ 2.12)	/	/	/	/	/
End-tidal carbon dioxide	0.03	0.07	0.47	0.640	1.03(0.90 ~ 1.18)	/	/	/	/	/
At the end of surgery										
Driving pressure	0.16	0.08	2.04	0.042	1.17(1.01 ~ 1.36)	/	/	/	/	/
Peak inspiratory pressure	−0.07	0.09	−0.80	0.422	0.93(0.78 ~ 1.11)	/	/	/	/	/
Positive end-expiratory airway pressure	−0.04	0.14	−0.26	0.793	0.96(0.73 ~ 1.27)	/	/	/	/	/
Tidal volume	0.01	0.01	1.81	0.070	1.01(1.00 ~ 1.02)	0.01	0.01	0.86	0.388	1.01 (0.99 ~ 1.02)
Respiratory rate	−0.08	0.24	−0.34	0.733	0.92(0.58 ~ 1.47)	/	/	/	/	/
Dynamic respiratory system compliance	0.04	0.03	1.16	0.246	1.04(0.98 ~ 1.10)	/	/	/	/	/
SpO_2	−0.65	0.25	−2.65	0.008	0.52(0.32 ~ 0.84)	−0.66	0.31	−2.11	0.035	0.52(0.28 ~ 0.95)
End-tidal carbon dioxide	−0.05	0.06	−0.78	0.433	0.95(0.85 ~ 1.07)	/	/	/	/	/

Table 5. Logistic regression analysis for the risk factor of postoperative pulmonary complications.

Data availability

The data from this study will not be shared publicly. All data included in this study are available upon request by contact with the corresponding author.

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Author contributions

Mei-fang Chen: Data curation and visualisation. Lin-fen Xie: Software. Xin-fan Lin: Validation. Ping-ping Wu: Methodology and Supervision. Jia-xin Zhang: Investigation. Liang-wan Chen: Supervision, writing, reviewing, and editing. Yong Lin: Writing-original draft preparation and conceptualisation.

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Declarations

Ethics approval and consent to participate

This prospective study followed the Declaration of Helsinki and was approved by the local ethics committee at Fujian Medical University Union Hospital (2022YF022-01), and all participants provided written informed consent.

Competing interests

The authors declare no competing interests.

Organs/tissues statement

No organs/tissues were procured from prisoners.

Additional information

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