BMC Anesthesiology

RESEARCH

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The impact of different inspired oxygen concentrations combined with nebulized prostaglandin E1 on oxygenation in patients undergoing one-lung ventilation: a randomized controlled trial

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Abstract

Background One-lung ventilation (OLV) requires a high inspired oxygen concentration (FiO_2) to promote oxygenation improvement, yet it increases the risk of postoperative pulmonary complications. Therefore, this study aimed to investigate the effects of prostaglandin E_1 (PGE_1) in reducing FiO_2 during general anesthesia and mechanical ventilation on oxygenation and postoperative complications in patients undergoing OLV.

Method A total of 120 patients scheduled for elective left thoracotomy esophageal cancer surgery were randomly divided into four groups ($n=30$): Group L ($FiO_2=0.4$, $PGE_1=0.1$ μg /kg), Group M ($FiO_2=0.5$, $PGE_1=0.1$ μg /kg), Group H ($FiO_2=0.6$, $PGE_1=0.1$ μg /kg), and Group C ($FiO_2=0.4$, normal saline solution). The primary outcome was oxygenation during OLV. Secondary outcomes included intrapulmonary shunt (Qs/Qt), incidence of postoperative pulmonary complications, and changes in inflammatory cytokines.

Results Group H exhibited higher PaO_2 values than Groups L, M, and C at all time points T1-T6. Group M also showed higher PaO_2 values than Groups L and C at all time points T1-T6. In contrast, Group L demonstrated significantly higher PaO_2 values than Group C at time points T2-T4. The nebulization groups (L, M, H) had significantly higher PaO_2/FiO_2 than Group C at time points T2-T4. Group H had higher Qs/Qt values than Groups L, M, and C at all time points T1-T6. At time points T2-T4, Group L had significantly lower Qs/Qt values compared to both Group C and Group M, which in turn had significantly lower values than Group C. Regarding interleukin-6 (IL-6) levels, Group C was significantly higher than the nebulization groups at time points T5-T8, while Group L was significantly lower than Groups M and H at T8. In terms of tumor necrosis factor-α(TNF-α) levels, Group C was significantly higher than the nebulization groups at time points T7-T8. With respect to clinical pulmonary infection score (CPIS), Group L was significantly lower than Groups

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M, H, and C. There was no statistically significant difference in the overall incidence of postoperative complications probability (PPCs) among the four groups, nor were there statistically significant differences in pneumothorax, pulmonary infection, anastomotic leakage, ICU stay duration, or total hospital stay duration among the groups.

Conclusion PGE_1 demonstrates a significant advantage in reducing the incidence of hypoxemia, effectively improving oxygenation status in patients undergoing OLV with lower FiO_2. Given the effects of PGE_1 on oxygenation and inflammatory factors, as well as the CPIS, the results of this study suggest that a clinical regimen of 0.4 FiO_2 + 0.1 μg /kg PGE_1 is appropriate.

Trial registration Chictr.org.cn identifier: Retrospectively registered, ChiCTR1800018288(09/09/2018).

Keywords Prostaglandin E_1, One-lung ventilation, Inspired oxygen concentration

Background

One-lung ventilation (OLV) is widely employed in the anesthesia process for thoracic surgery. During OLV, the ventilation-receiving lung exhibits reduced compliance due to the gravitational influence of the mediastinum and the elevated diaphragm in the lateral decubitus position. Meanwhile, although the non-ventilated lung remains unventilated, certain blood perfusion increases intrapulmonary shunt (Qs/Qt). These factors may augment the risk of intraoperative hypoxemia in patients. Therefore, during OLV, pure oxygen or high inspired oxygen concentration (FiO_2) are typically used to maintain patient oxygenation [1]. Current lung-protective ventilation strategies recommend reducing the FiO_2 as much as possible while ensuring adequate oxygenation, although the specific concentration remains undefined [2].

Prostaglandin E_1 (PGE_1), a selective pulmonary artery dilator, has been previously shown to effectively reduce Qs/Qt and significantly improve oxygenation when nebulized and inhaled into the ventilated lung prior to OLV, with minimal impact on hemodynamics [3]. This study aims to investigate the effects of PGE_1 on lowering the FiO_2 during general anesthesia and mechanical ventilation on oxygenation and postoperative complications in patients undergoing OLV.

Methods

Study population

A total of 120 patients with esophageal cancer scheduled for radical resection at the Affiliated Cancer Hospital of Nanjing Medical University between 2019 and 2023 were enrolled. Pathology confirmed esophageal cancer diagnoses. All participating patients or their families provided informed consent. Study subjects included 120 patients scheduled for left thoracotomy esophageal cancer radical surgery, aged 18–79 years, with a Body mass index (BMI) of 18–29.9 kg/m² and American Society of Anesthesiologists (ASA) II or III. Exclusion criteria included: [1] history of pulmonary surgery, immunotherapy, or neoadjuvant chemotherapy; [2] preoperative severe dysfunction of the heart, liver, or kidneys; [3] severe complications such as hypertension, coronary heart disease, or glaucoma; [4] withdrawal from the study at any stage; [5] intraoperative severe arrhythmia or circulatory instability; [6] surgical duration less than 2 or more than 6 h; [7] failure to maintain $SpO_2 \geq 90\%$ during surgery, defined as either failure to restore SpO_2 to ≥ 90% within 3 min of desaturation or subsequent decline to < 88%.

All patients were randomly assigned to 1 of 4 groups using a computer-generated random number table: Group L ($FiO_2 = 0.4$, $PGE_1 = 0.1$ μg /kg), Group M ($FiO_2 = 0.5$, $PGE_1 = 0.1$ μg /kg), Group H ($FiO_2 = 0.6$, $PGE_1 = 0.1$ μg /kg), or Group C ($FiO_2 = 0.4$, normal saline solution). The randomization sequence was generated by an independent biostatistician. Participants and investigators (including treating physicians, nurses, and outcome assessors) remained blinded to group assignments. Data collection was conducted by blinded research team members, ensuring objectivity. An independent statistician who remained blinded until final analysis performed the unblinding and data analysis. All subjects enrolled provided written informed consent, and the study was approved by the Ethics Committee of Nanjing Medical University.

Anesthesia and intervention

All patients underwent ultrasound-guided right internal jugular vein catheterization and right radial artery catheterization under local anesthesia for pressure monitoring upon arrival in the operating room. Total intravenous anesthesia was administered without premedication. The anesthesia induction sequence included midazolam 0.05 $mg{\cdot}kg^{-1}$, fentanyl 3–4 $\mu g{\cdot}kg^{-1}$, propofol 1 $mg{\cdot}kg^{-1}$, and cisatracurium 0.2 $mg{\cdot}kg^{-1}$. A left double-lumen endobronchial tube was inserted under video laryngoscopy, with its position confirmed using a fiberoptic bronchoscope. Volume-controlled mechanical ventilation (VCV) was employed, with the anesthesia machine settings configured as follows: tidal volume (VT) 6–8 ml/kg (ideal body weight), PEEP 5 cmH_2O, respiratory rate 12–14 breaths per minute, inspiratory-to-expiratory ratio 1:2. The RR was adjusted to maintain end-tidal CO_2 ($ETCO_2$) between 35 and 45 cmH_2O, and FiO_2 was set according to the respective study group. If SpO_2 dropped

below 90% during one-lung ventilation (OLV) and persisted for more than 3 min or further decreased to less than 88%, the following interventions were sequentially applied: increasing FiO_2 to 100%, applying continuous positive airway pressure (CPAP) to the non-ventilated lung, and if necessary, restoring two-lung ventilation. During the maintenance phase of anesthesia, intravenous infusion of propofol at a rate of 0.04–0.06 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$, remifentanil at 0.2 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$, cisatracurium at 0.15 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$, and dexmedetomidine at 0.2 $\mu g{\cdot}kg^{-1}{\cdot}h^{-1}$ was administered. Intraoperative warming was maintained using an inflatable warming blanket to ensure nasopharyngeal temperature remained above 36 ℃. Blood pressure fluctuations were kept within 20% of the baseline value, with vasoactive drugs used as necessary to regulate blood pressure. After stable anesthesia, the patient was positioned in the right lateral decubitus position, and a fiberoptic bronchoscope was used to confirm the correct placement of the double-lumen tube.

Nebulization was then initiated, with Group L, M, and H receiving PGE_1 (brand name: Alprostadil Injection) nebulization (0.1 μg/kg diluted in 10 ml of normal saline solution) to the right lung, while Group C received ultrasonic nebulization of 10 ml of normal saline solution to the right lung. The dose of 0.1 μg/kg PGE_1 was chosen based on previous studies [3] demonstrating its efficacy in improving oxygenation and reducing inflammatory responses in patients undergoing OLV. The nebulization flow rate was set at 2 L/min, and the nebulization duration was 10 min to ensure complete nebulization of all fluids. After the onset of OLV, the VT was adjusted to 4–6 ml/kg (ideal body weight), while other respiratory parameters remained unchanged. During chest closure, manual lung recruitment was performed to restore two-lung ventilation (with airway pressure limited to below 30 cmH_2O for 30 s), and all patients were transferred to the ICU at the end of the surgery.

Observed indicators

The surgical duration, OLV duration, blood loss, urine output, and fluid intake of patients were recorded. Blood samples were collected from the radial artery and the right internal jugular vein for blood gas analysis at the following time points: before anesthesia induction (T0), post-anesthesia/pre-nebulization (T1), OLV 10 min (T2), OLV 15 min (T3), OLV 30 min (T4), OLV 60 min (T5), and OLV 120 min (T6). The following parameters were recorded at each time point: PaO_2, SaO_2, $PaCO_2$, PvO_2, SvO_2, and the Qs/Qt, which was calculated using the formula: $Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$, where $CaO_2 = (1.36 * Hb * SaO_2) + (0.0031 * PaO_2)$, $CvO_2 = (1.36 * Hb * SvO_2) + (0.0031 * PvO_2)$, and $CcO_2 = [FiO_2 * (P_B - P_{H2O}) - PaCO_2 / R] * 0.0031 + (1.36 * Hb)$, with $P_B = 760$ mmHg, $P_{H2O} = 47$ mmHg, and $R = 0.8$. Additionally, the $ETCO_2$, MAP, Ppeak, HR and PaO_2/FiO_2 at each time point were recorded.

Central venous blood samples were collected at T0, T5, T7 (30 min after two-lung ventilation), and T8 (24 h post-surgery). The concentrations of serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured using the ELISA method. The clinical pulmonary infection score (CPIS) on post-operative day 2, ICU stay duration, total hospital stay, and pulmonary complications within the first seven post-operative days were also recorded.

Statistical analysis

Using PASS 2021, we calculated the sample size based on the PaO2 of each group during the pre-experiment OLV30min, taking $\alpha = 0.05$ and $1\text{-}\beta = 0.9$. This time point was selected as the primary endpoint because it represents the critical phase of hypoxemia risk during OLV. A minimum of 24 patients per group is required to achieve a power of 0.8 and a two-sided Alpha level of 0.05. Considering a 20% dropout rate, a final total of 30 patients was included in each group. Data analysis was performed using SPSS 27.0 software. Measurement data are expressed as mean ± standard deviation (M ± SD), and inter-group analysis was conducted using one-way ANOVA, Kruskal-Wallis test, or three-factor repeated measures ANOVA, depending on the situation. Additionally, the Student-Newman-Keuls (SNK) method was used to compare groups at different time points. Count data were analyzed using the chi-square test or Fisher's exact probability method. A P-value of less than 0.05 was considered statistically significant.

Outcomes

The primary outcome was oxygenation during one lung ventilation (OLV), including PaO_2 measured at T2–T6. Secondary outcomes included Qs/Qt and PaO_2/FiO_2 during OLV, IL-6 and TNF-α levels at T1, T2, T7, and T8, CPIS, postoperative complications probability (PPCs), intensive care unit (ICU) stay duration, and total hospitalization time.

Results

Baseline characteristics

This study included 120 patients (88 males, 23 females), mean age 63.46 ± 6.26 years, randomly assigned to four groups. Six cases of hypoxemia occurred in Group C, one in Group L. Seven patients were excluded, resulting in a final sample of 113 patients (Fig. 1). There were no statistically significant differences in gender, age, ASA classification, BMI, preoperative PaO_2, surgery duration, or OLV duration among the four groups (Table 1).

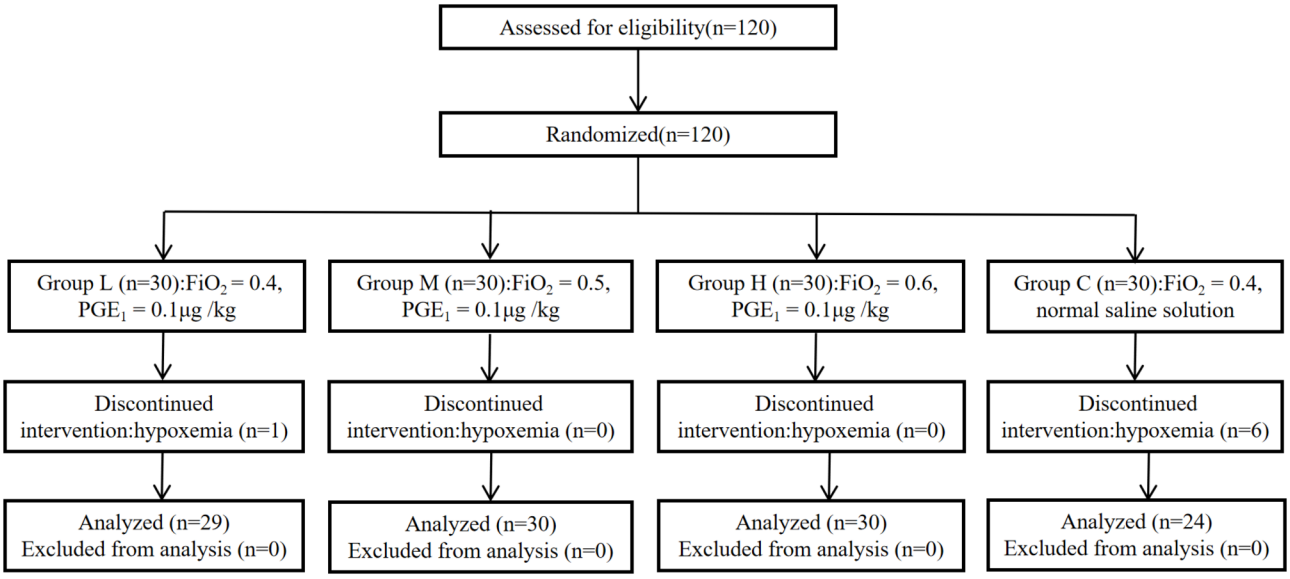

Fig. 1 Flow diagram of study participants

Table 1 Characteristic of patients with esophageal cancer [Mean ± SD / n(%)]

Characteristic	L group($n=29$)	M group($n=30$)	H group($n=30$)	C group($n=24$)
Male[#]	22(75.9)	25(83.3)	23(76.7)	19(79.2)
Female[#]	7(24.1)	5(16.7)	7(23.3)	5(20.8)
Age, year[*]	63.3 ± 6.5	63.2 ± 5.4	62.8 ± 6.8	64.5 ± 7.6
ASA II[#]	22(75.9)	24(80)	21(70)	20(83.3)
ASA III[#]	7(24.1)	6(20)	9(30)	4(16.7)
BMI, kg/m^2[*]	22.9 ± 2.8	23.6 ± 2.6	23.3 ± 3.2	22.4 ± 2.8
Preoperative PaO_2, mmHg[*]	80.1 ± 8.0	81.4 ± 7.5	78.4 ± 10.4	79.3 ± 9.5
Duration of surgery, min[*]	214.3 ± 45.9	215.2 ± 46.8	208.9 ± 58.9	210.0 ± 54.6
Duration of OLV, min[*]	177.3 ± 44.2	172.1 ± 46.6	171.3 ± 46.3	175.8 ± 47.6

"#" uses chi-square test; "*" uses one-way ANOVA; BMI, Body mass index; OLV, one-lung ventilation; L, 0.4 FiO_2 + 0.1 μg /kg PGE_1; M, 0.5 FiO_2 + 0.1 μg/kg PGE_1; H, 0.6 FiO_2 + 0.2 μg/kg PGE_1; C, 0.4 FiO_2 + normal saline solution.

Effects of PGE_1 on oxygenation under different FiO_2 levels

Within the first 30 min after the start of OLV, PaO_2 and PaO_2/FiO_2 decreased rapidly, while Qs/Qt gradually increased. PaO_2 and PaO_2/FiO_2 reached their lowest points at 60 min of OLV in the nebulized groups L, M and H, whereas the lowest point in the control group C occurred at 30 min (Table 2; Figs. 2 and 3). Qs/Qt peaked at 60 min of OLV in the nebulized groups L, M and H, but peaked at 30 min in the control group C (Table 2; Fig. 4). Throughout OLV, PaO_2 in the H group was higher than that in the groups L, M, and C at all time points. PaO_2 in the group M was higher than that in the groups L and C at all time points. PaO_2 in the group L was significantly higher than that in the group C between T2 and T4. (Table 2; Fig. 2). The PaO_2/FiO_2 in the nebulized groups L, M and H was significantly higher than that in the group C between T2 and T4 (Table 2; Fig. 3). Qs/Qt in the group H was higher than that in the groups L, M, and C at all time points. Between T2 and T4, Qs/Qt in the group L was significantly lower than that in the groups C and M, and Qs/Qt in the group M was significantly lower than that in the group C (Table 2; Fig. 4). There were no significant differences in $PaCO_2$, $PETCO_2$, Ppeak, MAP and HR among the four groups at all time points (Table 3).

Effects of PGE_1 on inflammatory factors and postoperative pulmonary complications under different FiO_2 levels

Regarding IL-6 levels, the group C showed significantly higher levels at T5, T7, and T8 compared to the nebulized groups L, M and H (Table 4). At T8, IL-6 levels in the group L were significantly lower than those in the groups M and H, with no statistical differences at other time points. Regarding TNF-α levels, the group C exhibited significantly higher levels at T7 and T8 compared to the nebulized groups L, M and H, while there were no statistical differences among the groups L, M, and H (Table 4). In terms of postoperative CPIS, the group L had significantly lower scores than the groups M, H, and C. There were no statistically significant differences in

Table 2 The levels of PaO_2, PaO_2/FiO_2, Qs/Qt among four groups (Mean ± SD)

Indicator	Group	T_1	T_2	T_3	T_4	T_5	T_6
PaO_2,mmHg*							
	L	172.7 ± 51.1	100.4 ± 25.6[a]	90.2 ± 29.4[a]	85.7 ± 15.3[a]	79.8 ± 16.9	100.5 ± 24.6
	M	242.5 ± 41.2[ab]	129.5 ± 56.5[ab]	111.5 ± 30.4[ab]	105.8 ± 28.3[ab]	100.8 ± 38.0[ab]	115.6 ± 32.6[ab]
	H	273.4 ± 32.4[abc]	151.4 ± 34.2[abc]	134.4 ± 29.4[abc]	124.2 ± 24.1[abc]	116.4 ± 33.5[abc]	152.8 ± 46.2[abc]
	C	177.3 ± 51.5	82.4 ± 24.0	76.7 ± 13.0	71.6 ± 12.5	79.5 ± 14.7	101.9 ± 24.3
PaO_2/FiO_2, mmHg*							
	L	434.8 ± 122.2	250.0 ± 63.9[a]	225.4 ± 73104.4[a]	201.8 ± 33.5[a]	199.5 ± 42.3	246.6 ± 60.2
	M	481.7 ± 89.2	254.5 ± 55.8[a]	221.6 ± 72.3[a]	210.8 ± 54.6[a]	202.7 ± 73.0	231.7 ± 65.5
	H	454.3 ± 61.3	253.3 ± 52.68[a]	219.6 ± 45.4[a]	200.6 ± 45.5[a]	192.4 ± 58.3	253.6 ± 77.8
	C	443.3 ± 128.7	205.9 ± 60.1	191.8 ± 32.7	178.9 ± 31.2	198.7 ± 36.7	254.8 ± 60.7
Qs/Qt*							
	L	7.50 ± 2.3	12.8 ± 1.7[a]	13.5 ± 2.0[a]	14.4 ± 1.6[a]	15.8 ± 2.0	14.4 ± 2.7
	M	8.4 ± 2.4	14.4 ± 2.4[ab]	15.4 ± 1.8[ab]	15.6 ± 1.3[ab]	16.0 ± 1.5	15.2 ± 1.6
	H	11.7 ± 1.5[abc]	16.6 ± 1.6[abc]	17.6 ± 1.4[abc]	18.8 ± 1.2[abc]	19.3 ± 1.2[abc]	17.5 ± 1.4[abc]
	C	8.0 ± 2.6	15.5 ± 2.7	16.2 ± 2.9	17.1 ± 2.7	16.3 ± 2.1	15.5 ± 1.9

"*" uses one-way ANOVA; T1, post-anesthesia/pre-nebulization; T2, OLV 10 min; T3, OLV 15 min; T4, OLV 30 min; T5, OLV 60 min; T6, OLV 120 min; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L, [c]$P<0.05$ compared with Group M.

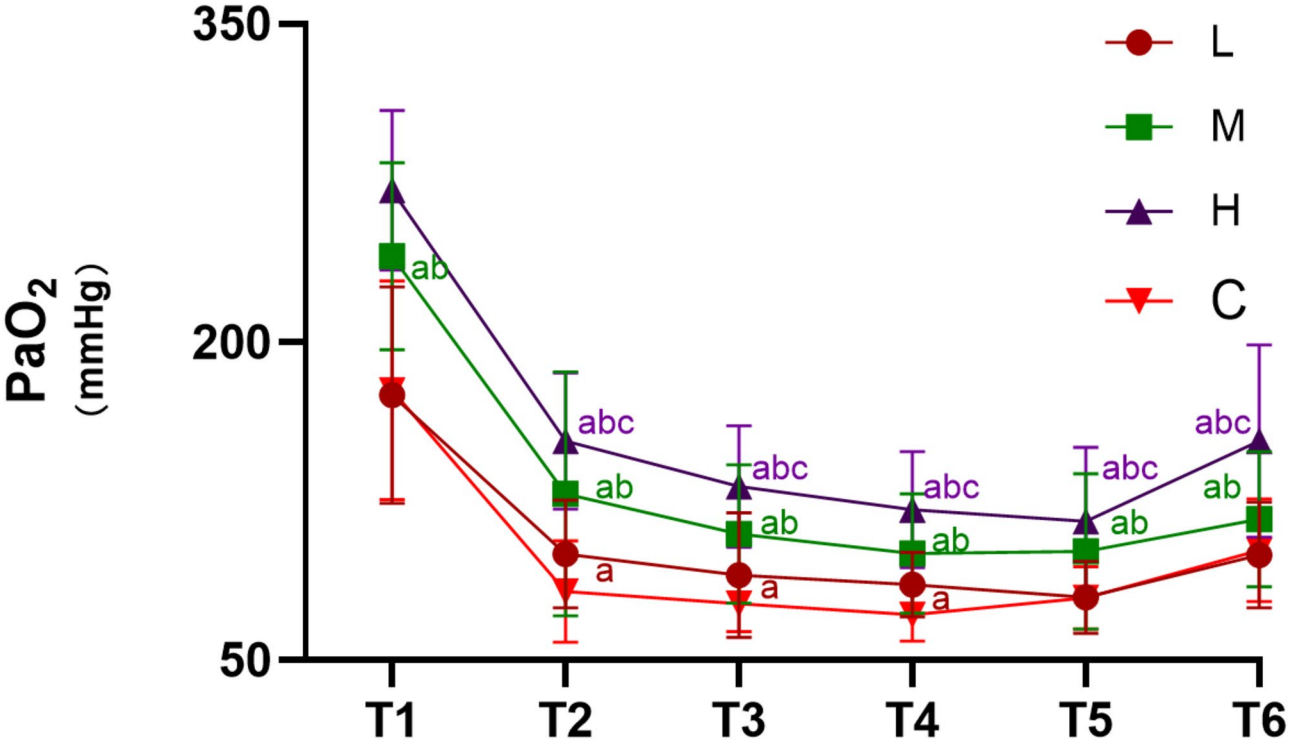

Fig. 2 PaO_2 dynamic changing during OLV in four groups. "PaO_2" uses one-way ANOVA; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L, [c]$P<0.05$ compared with Group M

the overall incidence of PPCs among the four groups, nor were there differences in atelectasis, pulmonary infections, anastomotic leaks, ICU stay duration, or total hospital stay among the groups (Table 5).

Discussion

During OLV, the core elements of anesthesia management include adequate oxygenation and lung protection. Effectively reducing the risk of hypoxemia during OLV and minimizing oxidative stress damage caused by high FiO_2 are two critical yet seemingly contradictory aspects of lung protection research during OLV [4, 5]. Regarding the appropriate level of FiO_2 during OLV, clear clinical

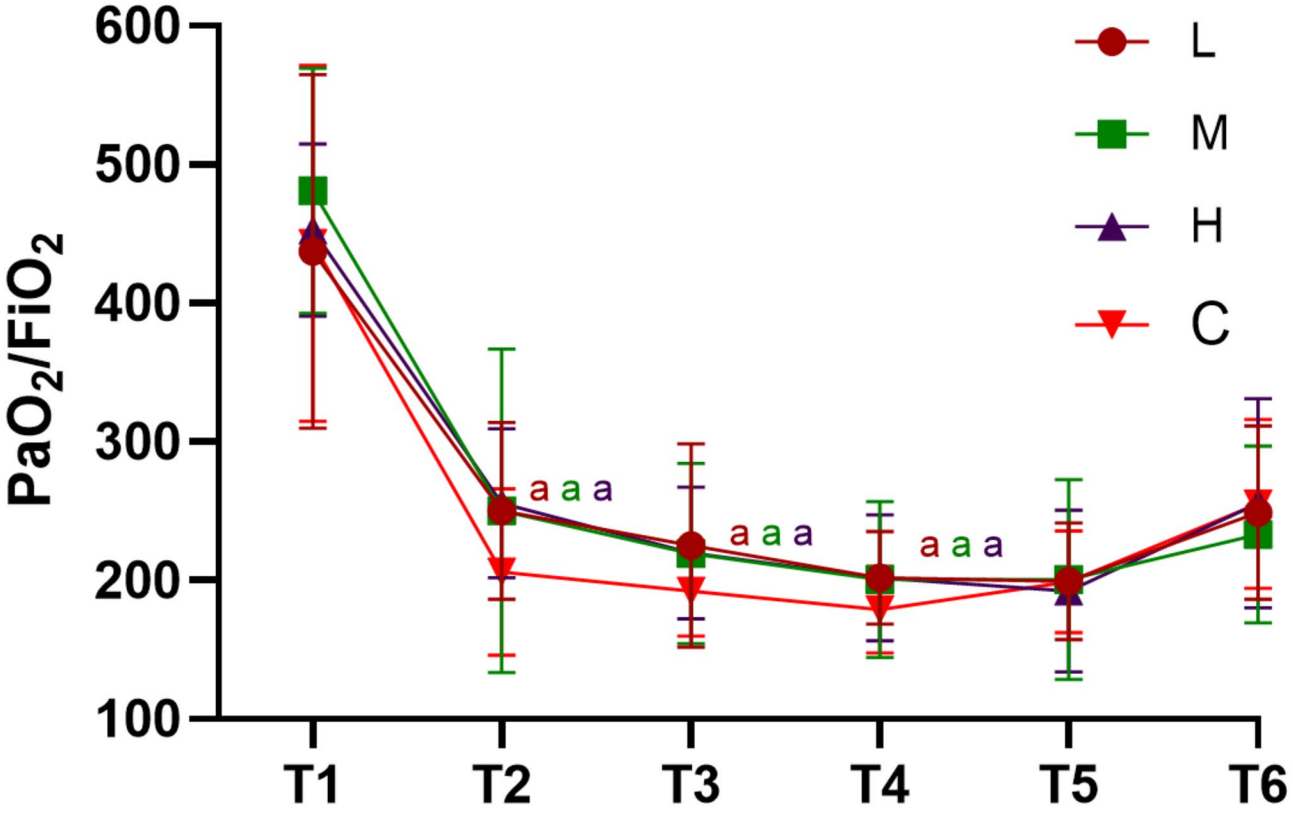

Fig. 3 PaO_2 /FiO_2 dynamic changing during OLV in four groups. "PaO_2/FiO_2" uses one-way ANOVA; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L, [c]$P<0.05$ compared with Group M

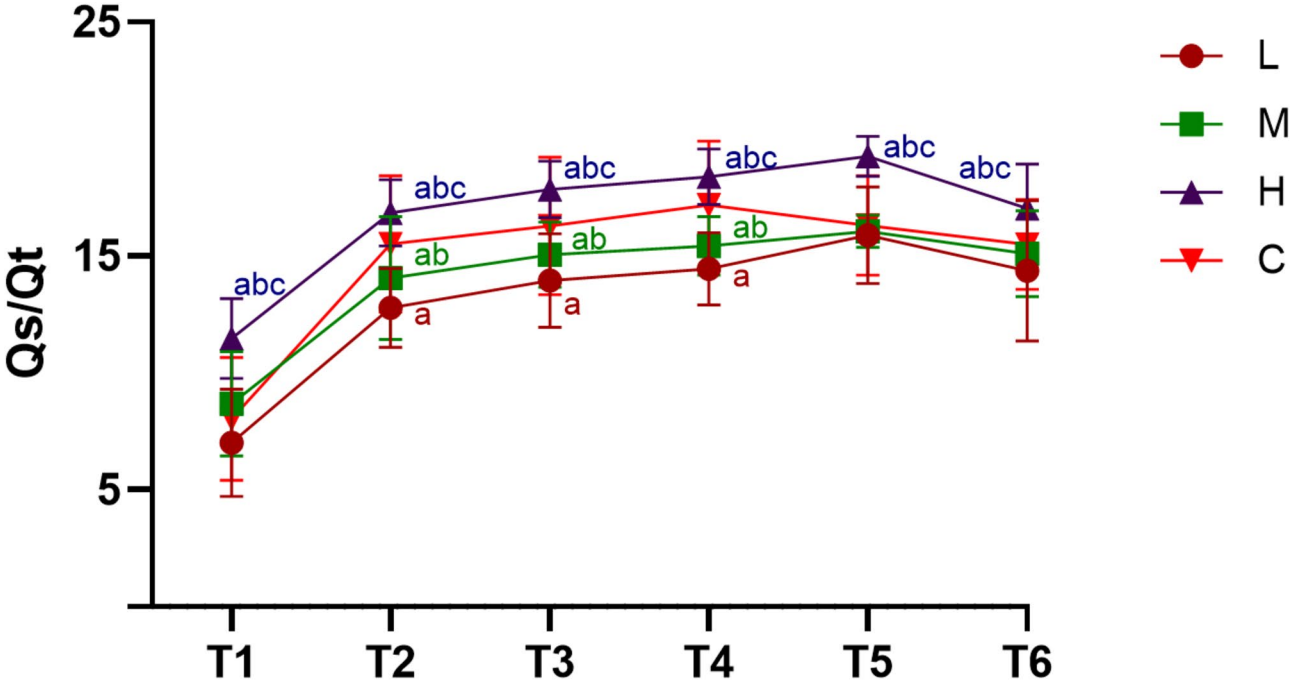

Fig. 4 Qs/Qt dynamic changing during OLV in four groups. "Qs/Qt" uses one-way ANOVA; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L, [c]$P<0.05$ compared with Group M

Table 3 The levels of SaO_2, $PaCO_2$, $ETCO_2$, Ppeak, MAP, HR among four groups(Mean ± SD)

Indicator	Group	T_1	T_2	T_3	T_4	T_5	T_6
SaO_2, %*							
	L	99.2 ± 0.8	95.3 ± 2.4	95.2 ± 2.7	93.5 ± 3.2	95.1 ± 2.0	97.3 ± 1.6
	M	99.9 ± 0.4	96.9 ± 2.7[ab]	96.4 ± 2.5[ab]	95.9 ± 3.0[ab]	96.2 ± 2.9[ab]	97.6 ± 2.1
	H	100 ± 0.0	98.7 ± 1.0[abc]	98.3 ± 1.4[abc]	98.3 ± 1.4[abc]	98.0 ± 1.3[abc]	98.8 ± 1.5[ab]
	C	99.3 ± 0.3	95.4 ± 1.1	95.5 ± 2.2	93.0 ± 3.1	95.4 ± 2.1	97.3 ± 1.6
$PaCO_2$, mmHg*							
	L	46.2 ± 18.1	46.3 ± 7.2	43.8 ± 4.9	42.5 ± 5.2	40.9 ± 6.1	39.4 ± 4.7
	M	40.6 ± 3.2	41.1 ± 5.7	39.4 ± 5.6	40.1 ± 6.1	42.2 ± 6.2	38.4 ± 5.7
	H	42.9 ± 6.0	43.3 ± 6.2	41.8 ± 5.8	40.1 ± 5.8	41.6 ± 6.3	39.5 ± 6.8
	C	42.5 ± 4.4	41.5 ± 5.9	41.3 ± 5.3	41.3 ± 5.8	40.4 ± 6.3	39.7 ± 5.4
$ETCO_2$, mmHg*							
	L	35.2 ± 3.6	36.3 ± 4.7	35.6 ± 4.0	33.9 ± 4.6	33.1 ± 4.4	33.6 ± 3.3
	M	34.5 ± 3.8	38.1 ± 3.6	36.7 ± 3.6	36.5 ± 4.2	36.4 ± 4.5	36.3 ± 4.9
	H	35.4 ± 5.8	36.8 ± 4.6	35.7 ± 4.1	34.7 ± 4.0	35.1 ± 4.4	34.4 ± 4.4
	C	35.6 ± 5.3	36.6 ± 4.2	36.0 ± 4.1	35.3 ± 3.6	35.4 ± 3.8	34.1 ± 4.0
Ppeak, cmH_2O*							
	L	15.1 ± 3.7	21.9 ± 4.9	21.4 ± 4.9	22.1 ± 5.9	21.8 ± 4.9	22.0 ± 3.5
	M	14.9 ± 3.2	22.5 ± 3.7	23.0 ± 3.4	23.6 ± 4.5	24.3 ± 4.5	24.3 ± 3.9
	H	14.9 ± 3.2	22.5 ± 3.7	23.0 ± 3.4	23.6 ± 4.5	24.3 ± 4.5	24.3 ± 3.9
	C	14.4 ± 2.6	23.1 ± 3.9	23.2 ± 3.4	23.7 ± 3,9	24.6 ± 3.8	24.9 ± 4.5
MAP, mmHg*							
	L	97.6 ± 13.1	98.1 ± 13.0	94.2 ± 13.4	96.7 ± 11.2	100.4 ± 10.2	98.8 ± 12.1
	M	97.6 ± 13.1	98.1 ± 13.0	94.2 ± 13.4	96.7 ± 11.2	100.4 ± 10.2	98.8 ± 12.1
	H	102.2 ± 14.6	96.6 ± 16.0	92.7 ± 16.2	94.2 ± 22.8	95.7 ± 21.2	95.4 ± 16.4
	C	98.4 ± 12.2	98.3 ± 13.1	92.8 ± 12.8	98.2 ± 11.1	100.9 ± 9.8	98.3 ± 12.9
HR, bpm*							
	L	82.7 ± 13.6	78.3 ± 15.7	75.6 ± 13.7	78.3 ± 13.9	78.8 ± 14.1	76.4 ± 12.4
	M	74.0 ± 10.0	73.9 ± 14.8	73.7 ± 13.0	72.1 ± 12.8	71.8 ± 11.6	70.0 ± 11.2
	H	76.6 ± 14.5	73.7 ± 14.7	74.4 ± 14.4	82.7 ± 12.7	78.8 ± 13.6	75.9 ± 13.9
	C	77.1 ± 10.5	74.2 ± 14.3	75.7 ± 13.1	77.7 ± 9.8	79.0 ± 13.4	74.3 ± 10.7

"*" uses one-way ANOVA; T1, post-anesthesia/pre-nebulization; T2, OLV 10 min; T3, OLV 15 min; T4, OLV 30 min; T5, OLV 60 min; T6, OLV 120 min; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L; [c]$P<0.05$ compared with Group M.

Table 4 Serum levels of IL-6 and TNF-αin the four groups (Mean ± SD)

Biomarkers	Group	T_1	T_5	T_7	T_8
IL-6, pg/mL*	L	4.96 ± 2.49	23.86 ± 4.97[a]	39.53 ± 6.84[a]	58.54 ± 15.41[a]
	M	4.95 ± 2.43	23.82 ± 5.15[a]	39.65 ± 6.61[a]	67.69 ± 9.17[ab]
	H	5.15 ± 2.76	23.78 ± 4.51[a]	38.45 ± 10.59[a]	67.97 ± 7.22[ab]
	C	4.14 ± 2.57	34.80 ± 7.35	84.4 ± 15.72	109.63 ± 17.47
TNF-α, pg/mL*	L	0.82 ± 0.23	1.88 ± 0.4	2.66 ± 0.45[a]	3.3 ± 0.86[a]
	M	0.86 ± 0.41	1.74 ± 0.52	2.49 ± 0.54[a]	3.09 ± 0.50[a]
	H	1.00 ± 0.40	1.87 ± 0.91	2.68 ± 0.70[a]	3.02 ± 0.65[a]
	C	1.00 ± 0.29	1.77 ± 0.83	3.53 ± 0.79	4.63 ± 0.71

"*" uses one-way ANOVA; [a]$P<0.05$ compared with Group C; [b]$P<0.05$ compared with Group L; T1, post-anesthesia/pre-nebulization; T5, OLV 60 min; T7, 30 min after two-lung ventilation; T8, 24 h post-surgery; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

guidelines are currently lacking. When performing OLV, a protective ventilation strategy should strictly control FiO_2. While ensuring adequate oxygenation, efforts should be made to maintain FiO_2 at the lowest possible level. FiO_2 reduction should start from a baseline below 1.0 to mitigate oxidative stress damage exacerbated by high-concentration oxygen inhalation [5]. This study demonstrates that pre-OLV administration of 0.1 μg/kg PGE_1 to the ventilated lung reduces the required FiO_2 during OLV. The reduction in FiO_2, combined with the physiological effects of PGE_1, not only contributes to a decrease in the Qs/Qt, improved oxygenation, and a lower incidence of hypoxemia but also reduces the release of inflammatory cytokines (IL-6, TNF-α), leading to a reduction in the CPIS.

Table 5 Postoperative rehabilitation of patients in the four groups [Mean ± SD / n(%)]

Characteristics	L	M	H	C
	29	30	30	24
CPIS*	1.8 ± 0.9	3.4 ± 1.2[b]	3.9 ± 1.8[b]	4.43 ± 1.3[b]
Atelectasis of lung$	0(0)	1(3.33)	2(6.67)	0 (0)
Pulmonary infection$	1(3.45)	1(3.33)	2(6.67)	1(4.55)
Anastomotic leakage$	1(3.45)	1(3.33)	1(3.33)	2 (9.10)
LOS in ICU, day*	1.1 ± 0.2	1.0 ± 0.0	1.0 ± 0.0	1.3 ± 0.6
LOS in hospital, day#	25.5 ± 7.8	23.2 ± 7.0	20.4 ± 2.4	27.3 ± 8.2

"*" uses one-way ANOVA; "$" uses Fisher's exact probability method; LOS, Length of stay; [b]$P<0.05$ compared with Group L.

Studies have indicated [6] that inhaling high FiO_2 during general anesthesia has adverse effects on the human body, and it is recommended to use ventilation with FiO_2 not exceeding 0.6. Additionally, ROCCA reported [7] that the minimum FiO_2 during OLV can be as low as 0.4. Therefore, the FiO_2 values set in this study were 0.4, 0.5, and 0.6. PGE_1 acts as a selective pulmonary vasodilator by activating adenylate cyclase, increasing cyclic AMP, and reducing intracellular calcium [8]. This preferentially dilates vessels in the ventilated lung, redirecting perfusion away from the non-ventilated lung and lowering Qs/Qt. Previous studies have reported that [3] PGE_1 can help maintain adequate oxygenation in OLV patients with FiO_2 0.6, but it remains unclear how low an FiO_2 PGE_1 can help OLV patients tolerate. Therefore, this study aimed to investigate the effects of different FiO_2 levels on oxygenation and Qs/Qt in OLV patients after pre-OLV nebulized inhalation of 0.1 μg/kg PGE_1 in the ventilated lung, to determine the optimal FiO_2 value.

Yang M et al. [9] reported that during OLV, 58% of patients undergoing protective strategies ($FiO_2 = 0.5$, PEEP = 5 cmH_2O, VT = 6 mL/kg) experienced hypoxemia ($SpO_2 < 95\%$) and required an increase in FiO_2 to maintain $SpO_2 > 95\%$. Similarly, this study observed that in the group C with FiO_2 0.4, 6 patients developed hypoxemia (SpO_2 dropped below 90% and failed to recover to ≥ 90% within 3 min or further decreased to < 88%), with an incidence rate of 25%, indicating a higher risk of hypoxemia in patients with FiO_2 0.4. In the group L, which received FiO_2 0.4 with PGE_1 nebulization, only one case of hypoxemia occurred, indicating that nebulized PGE_1 can significantly reduce the incidence of hypoxemia. This also demonstrates that under FiO_2 0.4 during OLV, nebulized PGE_1 in the ventilated lung can ensure adequate oxygen supply, thereby enabling a reduction in FiO_2 while maintaining oxygenation. Furthermore, in OLV patients receiving nebulized PGE_1, although PaO_2 and SaO_2 levels decreased when FiO_2 was reduced from 0.6 to 0.4, they remained within safe ranges. Additionally, we observed no significant differences in $PaCO_2$, $ETCO_2$, Ppeak, MAP, or HR levels among patients under FiO_2 0.6, 0.5, and 0.4. Therefore, nebulized 0.1 μg/kg PGE_1 in the ventilated lung enables OLV patients to safely tolerate FiO_2 0.4.

During OLV, the patient's physiological state undergoes the following changes: First, the non-ventilated lung fully collapses, receiving no ventilation but retaining some blood perfusion, resulting in Qs/Qt. Second, due to gravitational effects, the ventilated lung takes on most of the pulmonary blood flow and all the ventilation, leading to an imbalance in the ventilation-perfusion ratio (V/Q). Additionally, when the patient is in the lateral decubitus position, the compliance of the ventilated lung decreases due to the gravitational effect of the mediastinum and the elevation of the diaphragm. Finally, the non-ventilated lung undergoes hypoxic pulmonary vasoconstriction (HPV).During OLV, HPV serves as one of the body's self-regulatory protective mechanisms against hypoxia [10] and is particularly critical. The primary stimulus for this mechanism is alveolar oxygen tension, which induces pre-capillary vasoconstriction to reduce blood flow to hypoxic lung tissue. This reduces Qs/Qt, mitigates V/Q mismatch, and improves oxygenation. Under the influence of HPV, blood flow in hypoxic regions of the lung can be redirected to non-hypoxic areas, with a redistribution rate of up to 50-70% [11]. This mechanism plays a crucial role in reducing Qs/Qt, adjusting the V/Q, and improving oxygenation.

Studies indicate that under normal HPV function, blood perfusion in the non-ventilated lung can be reduced to 20-25% [12]. Further studies reveal the HPV effect becomes evident within 15 min of OLV, peaks at 60 min, and shows no significant changes thereafter [13–15]. In clinical practice, studies indicate [16] the Qs/Qt rises rapidly during the initial stage of OLV, reaching its peak at 30 min, accompanied by a rapid decline in arterial PaO_2, particularly between 15 and 30 min of OLV when PaO_2 drops to its lowest level. Subsequently, over the next 1–2 h, PaO_2 gradually rises. In this study, we found PaO_2 in all four groups decreased linearly within 30 min of OLV, with the group C reaching its lowest point at 30 min, and then gradually rising. This finding is consistent with previous research. After PGE_1 nebulization, the L, M, and H groups' lowest PaO_2 values were delayed until 60 min, when the HPV effect peaked. Therefore, pre-OLV ventilation-side lung nebulization with PGE_1 helps patients pass through the sharp decline in PaO_2 during the first 30 min of OLV, reducing hypoxemia occurrence.

Previous studies have demonstrated [10, 17] that HPV can improve the body's oxygenation function by reducing Qs/Qt. However, it is important to note that this regulatory effect of HPV is influenced by various factors, including anesthetic drugs, disease conditions, surgical procedures, and physiological factors [18], with FiO_2 being one important factor. This study found that from

anesthesia induction to OLV 30 min, Qs/Qt in the L, M, and H groups increased in a dose-dependent manner with increasing FiO_2, which may be related to enhanced inhibition of HPV as FiO_2 increases [8]. In addition, during the first 30 min after the start of OLV, Qs/Qt in the group L was significantly lower than in the group C. We speculate that the mechanism by which PGE_1 inhalation reduces Qs/Qt is mainly related to PGE_1 being a selective pulmonary artery vasodilator [19]. PGE_1 increases blood flow to the ventilated side of the lung, thereby reducing Qs/Qt.

Intravenous infusion of PGE_1 can reduce serum IL-6 and TNF-α levels, thereby alleviating organ inflammatory damage [20]. This study further observed the effect of inhaled PGE_1 on serum inflammatory factors. The results showed that inhalation of 0.1 μg/kg PGE_1 significantly reduced serum IL-6 levels at 30 min after OLV, 30 min after OLV completion, and 24 h postoperatively, as well as serum TNF-α levels at 30 min after OLV completion and 24 h postoperatively. Notably, IL-6 in the group L on the second postoperative day was also significantly lower than in the groups M and H. IL-6, as a pro-inflammatory factor with diverse biological functions, plays a crucial role in immune regulation and inflammatory responses in various pathophysiological processes. During the acute phase of injury and infection, the concentration of IL-6 in the blood typically increases significantly [21]. Breunig et al. [22] found that IL-6 levels in both serum and bronchoalveolar lavage fluid significantly increased after the completion of OLV. TNF-α is one of the pro-inflammatory factors involved in mediating acute lung injury, with functions such as inducing pulmonary endothelial cell activation, leukocyte migration, granulocyte degranulation, and capillary leakage. In addition, it can directly or indirectly inhibit the synthesis of pulmonary surfactant [23, 24]. Additionally, it is noteworthy that the CPIS in the L group was significantly lower than in the other three groups. CPIS is an assessment tool that integrates clinical manifestations, imaging features, and microbiological test results to evaluate the severity of pulmonary infection. However, due to the limited sample size, there were no statistically significant differences among the four groups in terms of postoperative atelectasis incidence, pulmonary infection incidence, anastomotic leak incidence, ICU stay duration, and total hospital stay.

Taking into account the effects of the aforementioned inflammatory factors and the comprehensive evaluation of postoperative CPIS, it is recommended to utilize 0.4 FiO_2 + 0.1 μg/kg PGE_1 as a superior nebulization combination. This combination not only ensures adequate oxygenation for the body, reduces Qs/Qt, and lowers the incidence of hypoxemia, but also shows promise in reducing the infection risk observed at the time points we monitored.

Limitation

However, several limitations of this study cannot be overlooked. Firstly, the sample size calculation was based on PaO_2 as the primary outcome measure rather than postoperative complications, which may lead to false-negative conclusions regarding the incidence of postoperative complications. Secondly, the nebulized dose of PGE_1 was set at 0.1 μg/kg, and higher doses of PGE_1 were not investigated. Lastly, our study population was limited to patients with normal lung function, and subjects with impaired lung function were not included. Therefore, whether the recommended combination (0.4 FiO_2 + 0.1 μg/kg PGE_1) is suitable for patients with impaired lung function, the elderly, or obese individuals remains to be further validated. Future studies should focus on exploring the effects of different doses of PGE_1, the long-term outcomes of patients, and the applicability of this regimen in different patient populations.

Conclusion

In conclusion, pre-OLV administration of 0.1 μg/kg PGE_1 to the ventilated lung enhances pulmonary vasodilation, thereby reducing the Qs/Qt, improving oxygenation, and lowering the incidence of hypoxemia. These effects collectively enable a reduction in the required FiO_2. The combined impact of FiO_2 reduction and physiological effects of PGE_1 may further attenuate systemic inflammatory cytokine levels (IL-6 and TNF-α), which is associated with improved CPIS.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03081-3.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Lingxi Xing and Paerhati Halisa were responsible for data collection as well as writing the article. Yuyan Ding was responsible for data analysis and writing of the manuscript. Yihu Zhou and Jiaqi chang was responsible for the statistical analysis. Xiaolan Gu and Lianbing Gu was responsible for guiding and reviewing the revision. All authors reviewed the manuscript.

Funding

Excellent Project of Jiangsu Cancer Hospital (YC201805).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All experiments were performed in accordance with relevant international and local guidelines and regulations. The study protocol was approved by the Ethics Committee of Nanjing Medical University. Informed consent

was obtained from all participants prior to conducting any study-related procedures. The study was conducted in strict compliance with the Helsinki Declaration. And this manuscript reporting adheres to CONSORT guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 17 February 2025 / Accepted: 17 April 2025
Published online: 06 May 2025

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