

The Effects of Inverse Ratio Ventilation with PEEP on Respiratory Function and Inflammatory Cytokines in Patients during One-lung Ventilation

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Abstract

Background: Hypoxemia is the most common complication during one-lung ventilation (OLV). Inverse ratio ventilation (IRV) may lead to intrinsic positive end-expiratory pressure (PEEP) and improve oxygenation in acute respiratory distress syndrome, so we investigated whether volume-controlled IRV with external PEEP could improve hypoxemia, reduce the risk of acute lung injury during OLV.

Methods: Sixty patients undergoing one-lung ventilation for open thoracotomy were randomly divided into IRV group and control group (n = 30). All patients were initially ventilated with a tidal volume of 8 mL/kg, an inspiratory: expiratory (I:E) ratio of 1:2 and a respiratory rate of 12 breaths/min in 100% oxygen without PEEP. During OLV, lungs were ventilated either with I:E of 2:1 (IRV group) or 1:2 (control group) with an actual tidal volume (VT) 7 mL/kg, respiratory rate 12 breaths/min, external PEEP of 5 cm H₂O. Arterial blood was collected respectively to analyze blood gas before and during OLV. Meanwhile, hemodynamic and respiratory mechanics were monitored. The concentrations of IL-1 β , IL-6 and IL-8 in bronchoalveolar lavage fluid (BALF) were measured before and during OLV.

Results: Compared to the control group, partial pressure of arterial oxygen (PaO₂), mean airway pressure and dynamic compliance (CL) were significantly higher in IRV group during OLV (P < 0.05). However, plateau pressure (P_{plat}) and levels of IL-1 β , IL-6 and IL-8 in BALF were lower in IRV group than those in control group (P < 0.05).

Conclusion: IRV (I:E = 2:1) applying PEEP could improve hypoxemia, promote oxygenation, and improve dynamic compliance of respiratory system, moreover reduce P_{plat} and the release of inflammatory cytokines in patients during one-lung ventilation. It is superior to conventional ventilation with PEEP during one-lung ventilation.

Keywords: Inverse ratio ventilation; One-lung ventilation; Hypoxemia; Lung injury

Introduction

The incidence of hypoxemia is reportedly from 5% to 10% during one-lung ventilation (OLV) [1]. High tidal volume and airway pressure during OLV correlated with the development of acute ventilation-induced lung injury in patients undergoing lung resection [2]. Inverse ratio ventilation (IRV) has been proposed for patients with adult respiratory distress syndrome to achieve adequate oxygenation [3,4], due to recruiting atelectatic alveoli [5,6], and it is reported that the optimal inspiratory to expiratory ratio (I:E) is 2:1 when using IRV [7]. It is widely accepted the use of low tidal volume should be accompanied by positive end-expiratory pressure (PEEP), and the previous study reported that PEEP could improve oxygenation [8,9], but it was rarely reported that IRV (I:E = 2:1) applying external PEEP was used in thoracic surgery. The present study tested the hypothesis that IRV (I:E = 2:1) applying external PEEP would improve hypoxemia, promote oxygenation and alleviate inflammation in patients underwent one-lung ventilation for lung lobectomy, is superior to conventional ventilation with PEEP. The primary endpoint was that IRV (I:E = 2:1) applying external PEEP would reduced P_{plat}.

Materials and Methods

This study was approved by the Hospital Ethics Committee of Jiaying maternity and child health care hospital and registered in protocol registration system (registration number: ChiCTR-IOR-15006517). The informed consent was signed before enrollment by the patients. From May 2015 to December 2015, we identified 60 patients undergoing elective lung lobectomy with ASA grade II, age 34-61 years, body mass index (BMI) 21-29 kg/m² and minute ventilation volume > 70 L/min to enroll in this study. We excluded the patients that had the history of

severe cardiovascular disease, asthma, chronic obstructive pulmonary disease and pneumothorax. There were 38 central type lung cancers and 22 peripheral type lung cancers among. The duration of the operation lasted 86.4-138.2 min. Sixty patients were randomly assigned to either control group (n = 30) or IRV group (n = 30) using computer-generated random number code.

Upon arrival in the operating room, standard monitoring including electrocardiogram, invasive arterial blood pressure (ABP), heart rate (HR), pulse oximetry (SpO₂) and central venous pressure (CVP) were applied and venous access was established. Anesthesia was induced with intravenous propofol 2 mg/kg, fentanyl 5 μ g/kg and rocuronium 0.6 mg/kg, then bronchial intubation was performed using direct laryngoscope. Anesthesia was maintained with propofol 6-10 mg \cdot kg⁻¹ \cdot h⁻¹ and remifentanyl 0.5-1 μ g \cdot kg⁻¹ \cdot min⁻¹ to keep the bispectral index (BIS) value between 40 to 55 (BIS monitor Model A2000, USA). The lungs were mechanically ventilated with ventilator (DATAX-OHMEDA Aspire anesthesia machine, USA). Muscle relaxation was monitored by the train-of-four (TOF) stimulation on the ulnar nerve (Organon, Type TOF-Watch SX, Holland). Continuous infusion of rocuronium was performed to

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maintain stable neuromuscular block.

The trachea was intubated using a double-lumen tube (37F for males and 39F for females), the correct position of the double-lumen tube was confirmed using a fiber-optic bronchoscope (Olympus company, Tokyo, Japan) after intubation in both supine and lateral positions. All patients were initially applied with two-lung ventilation. The lungs were initially ventilated using a constant-flow, volume-controlled ventilation mode with an actual tidal volume of 8 mL/kg actual body weight, an inspiratory to expiratory (I:E) ratio of 1:2, a respiratory rate of 12 breaths/min, oxygen flow rate of 1 L/min, and FiO_2 (fraction of inspiratory oxygen) of 1.0 without PEEP. OLV was initiated at the moment of skin incision, and the tube lumen of the non-ventilated lung was opened to room air. During OLV, tidal volume was reduced to 7 mL/kg, and ventilator settings were actual tidal volume (V_T) of 7 mL/kg, respiratory rate of 12 breaths/min, PEEP of 5 cm H_2O , FiO_2 (fraction of inspiratory oxygen) of 1.0, oxygen flow rate of 1 L/min, I:E of 2:1 (in IRV group) or 1:2 (in control group). At the time of closure of thoracic cavity, two-lung ventilation was started and both lungs were re-expanded by hand bagging in all patients.

Mean airway pressure (P_{mean}), plateau airway pressure (P_{plat}), total PEEP ($PEEP_{tot}$), dynamic compliance of respiratory system (CL) and end-tidal CO_2 partial pressure ($PetCO_2$) were monitored using a side-stream spirometry device (Anesthesia Monitor D-FPD15-00; GE, Taipei, Taiwan), maintaining $PetCO_2$ value of 35-45 mmHg. When $PetCO_2 > 45$ mmHg, tidal volume or breath rate was increased. All the patients were in lateral position with head down 10° during surgery. If SpO_2 was below 92% and lasted 30 seconds during OLV, surgery was temporarily interrupted and double-lung ventilation was alternately applied. The neuromuscular block was reversed with intravenous neostigmine 1 mg and atropine 0.5 mg when TOF $> 70\%$. Fentanyl 1 μ g/kg was administered for pain control at 30 min before the end of surgery. Postoperative complications were observed, such as time in Post Anesthesia Care Unit (PACU), time to extubation and incidence of hypoxemia. The Patient was discharged from PACU when the modified Aldrete score was appropriate (score ≥ 9) [10]. Patients were followed up for any complications of lung during their hospital stays. Throughout the perioperative operation, lactated Ringer's solution or hydroxyethyl starch solution was infused at rate of 8-10 mL \cdot kg $^{-1}\cdot$ h $^{-1}$.

Hemodynamic parameters, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), HR and CVP were recorded at 5 min before anesthesia induction (T0), 5 min after bronchial intubation (T1), the initiate of OLV (T2), 45 min of OLV (T3) and the end of surgery (T4), meanwhile, P_{mean} , P_{plat} , $PEEP_{tot}$ and CL were recorded at T1, T2, T3 and T4. Arterial blood gas and mixed venous blood gas were analyzed using a blood gas analyzer (ABL8000A, Denmark) and bronchoalveolar lavage fluid (BALF) of ventilated lung at T1 and T3 point. At T1 and T3 point, we collected bronchoalveolar lavage fluid performed by inflating 50 mL normal saline in ventilated lung and 20-40% this fluid was recovered with fiber bronchoscope (Olympus company, Tokyo, Japan), then samples were centrifuged at 3,000 rpm for 15 minutes at $4^\circ C$, saved for assay at $-70^\circ C$. IL-1 β , IL-6 and IL-8 levels were detected by enzyme-linked immunosorbent assay (ELISA), using the microplate reader (Hyperion MR III, USA). All enzyme-linked immunosorbent assays were performed according to the manufacturers' guidelines.

Statistical analysis

Descriptive statics and compliance with normal distribution was examined with one-sample Kolmogorov-Smirnov test. Between groups Student *t* test and Mann-Whitney *U*-test were used. Categorical variables were evaluated with the Chi-square test. Data were presented

as mean \pm standard deviation. Parametric data were checked for by using *t* test or categorical data was analyzed by Chi-square test. Significance was considered as *P* value < 0.05 . Data analysis was performed using the statistical software package SPSS 19.0 (SPSS Inc, Chicago, USA). Sample size based on a previous trial test. The main variable in the study, P_{plat} was having a standard deviation of 2.1 from a plot test done on 10 patients. A priori power analysis using two-sided analysis with an α -error of 0.05 and a power of 0.8 showed that 54 patients were needed for this study.

Results

No significant differences in age, body mass index, gender, maximal ventilation volume (MMV), time of OLV and operation time between groups (Table 1) ($P > 0.05$). At T3, PaO_2 increased significantly in IRV group, there was statistical significance between groups (Table 2) ($P < 0.01$). Comparison of pH, $PaCO_2$, SaO_2 and $ScvO_2$, there were no statistical significance in both groups ($P > 0.05$).

The P_{mean} , $PEEP_{tot}$ and CL were increased significantly in IRV group than those in control group at T1, T2, T3 and T4 (Table 3), there was statistically significant between groups ($P < 0.05$), but P_{plat} was lower in IRV group (Figure 1), there was statistical significance ($P < 0.05$). Hemodynamic monitoring reflects the hemodynamic changes in both groups (Figure 2). The comparison of hemodynamic parameters in both groups, there was no statistical significance ($P > 0.05$). The concentrations of IL-6, IL-8 and IL-1 β were lower in IRV group than those in the control group at T3, there was statistically significant between the groups ($P < 0.05$) (Table 3). Hypoxemia was 1 case in IRV group and 3 cases in control group during OLV (Table 1), however there was statistical significance between two groups ($P < 0.05$). There was no significance in the incidence of intraoperative hypoxemia and time in PACU between two groups ($P > 0.05$) (Table 1). No postoperative hypoxemia and hypoxemia was observed.

Discussion

One-lung ventilation is a common technique of ventilation in thoracic surgery, which is advantageous to surgical area because of the non-ventilated lung collapse, prevents from the secretions into the healthy lung and protects the healthy lung from pollution. Meanwhile the collapse lung will increase the intrapulmonary shunt, aggravate hypoxia and increase airway pressure of the ventilated lung to result in acute lung injury. High tidal volume and plateau pressure are the major risk factor of acute lung injury, thus the present study compared volume-controlled inverse ratio ventilation (I:E = 2:1) with PEEP to conventional volume-controlled ventilation (I:E = 1:2) with PEEP in patients undergoing one-lung ventilation.

Lower P_{plat} , higher P_{mean} , total PEEP and CL were observed in IRV group compared with the control group. Lower P_{plat} in IRV group was possibly because of the longer inspiratory time or slow inspiratory flow, and higher P_{mean} was achieved by moderate prolongation of I:E ratio [11]. Prolonging inspiratory time resulted in increases in P_{mean} and decreases in P_{peak} or P_{plat} in IRV group. Therefore, when applying low external PEEP, IRV is considered to be superior to conventional ratio ventilation in terms of gas exchange and respiratory mechanics in this study.

The mechanisms of improving oxygenation applying IRV were possibly as following: Firstly, P_{mean} is thought to be a major determinant because it is correlated with mean alveolar pressure and alveolar recruitment [11]. Secondly, increased inspiratory time may have enough time to gas exchange effectively. Lastly, PEEP was an important

Index	IRV	Control	P value
Age (year)	56.0 ± 13.1	54.3 ± 12.7	0.5198
BMI (kg/cm ²)	24.0 ± 3.2	23.4 ± 2.8	0.7254
Gender (male/female)	17/13	16/14	0.0671
MMV (L/min)	85.2 ± 11.8	87.4 ± 13.2	0.5014
Duration of OLV (min)	68.9 ± 12.6	73.1 ± 16.1	0.2694
Duration of operation (min)	116.5 ± 26.8	123.2 ± 31.6	0.3828
PACU discharge time (min)	57.2 ± 14.6	53.3 ± 13.2	0.2865
Intra-operative hypoxemia	1	3	0.7894

Data are mean ± SD or number. BMI: Body Mass Index; MMV: Maximal Ventilation Volume; PACU: Post Anesthesia Care Unit.

Table 1: Data of patients in both groups.

	IRV	Control	P value
Arterial blood gas at T1 point			
pH	7.37 ± 0.04	7.36 ± 0.02	0.1676
PaO ₂ (mmHg)	89.5 ± 7.8	91.6 ± 8.7	0.1994
PaCO ₂ (mmHg)	35.2 ± 2.8	34.5 ± 2.5	0.2476
SaO ₂ (%)	99.82 ± 0.13	99.79 ± 0.17	0.2749
ScvO ₂ (%)	68.7 ± 2.6	69.4 ± 2.8	0.2974
Arterial blood gas at T3 point			
pH	7.32 ± 0.06	7.34 ± 0.07	0.1802
PaO ₂ (mmHg)	232.7 ± 45.6	196.5 ± 35.5	0.0043*
PaCO ₂ (mmHg)	38.65 ± 5.4	36.87 ± 3.9	0.2407
SaO ₂ (%)	99.68 ± 1.8	99.56 ± 1.6	0.7549
ScvO ₂ (%)	77.9 ± 3.1	78.3 ± 3.4	0.7962

Data are mean ± SD, *Means statistically significant (p < 0.05). T1: At 5min after bronchial intubation; T3: At 45 min of one-lung ventilation; ScvO₂: Oxygen saturation of central venous blood.

Table 2: Arterial blood gas in both groups.

	IRV	Control	P value
At T1 point			
IL-1β (mp/L)	76.5 ± 14.5	72.8 ± 12.4	0.2967
IL-6 (mp/L)	118.6 ± 30.6	112.4 ± 23.1	0.3828
IL-8 (mp/L)	83.6 ± 17.9	80.4 ± 15.8	0.4686
At T3 point			
IL-1β (mp/L)	91.6 ± 21.2	106.7 ± 26.7	0.0215*
IL-6 (mp/L)	149.3 ± 34.6	177.8 ± 40.3	0.0063*
IL-8 (mp/L)	102.4 ± 22.4	117.7 ± 25.6	0.0197*

Data are mean ± standard deviation. Compared with the control group, *Means statistically significant (p < 0.05). T1: At the initiate of mechanical ventilation; T3: At 45 min of one-lung ventilation; IL: Interleukin.

Table 3: The levels of IL-1β, IL-6 and IL-8 in both groups (mp/L).

factor probably to improve oxygenation, which facilitated the mixing of gas, made collapse alveoli reopen and prevented atelectasis.

IRV would increase the P_{mean}, recruit atelectatic alveoli, reduce intrapulmonary shunt, improve ventilation-perfusion mismatch and decrease dead space ventilation [12]. Prolonged inspiratory time allows enough time to gas exchange. Meanwhile, as expiratory time was shorter, inverse ratio ventilation might lead to air trapping in the lungs with generation of auto-PEEP (internal PEEP). PEEP could increase the mean airway pressure and improve oxygenation. Documents are proved that IRV may lead to intrinsic PEEP [13] and is thought to improve oxygenation and to have advantageous effects on lung mechanics [14]. Higher mean airway pressure was benefit to gas exchange and prevented from lung collapse. PaCO₂ was showed modest decrease in IRV group compared to the control group, there was no significance between two groups. IRV didn't affect elimination of CO₂ [15], which was agreement with the present study that IRV with PEEP didn't prolong the time to

extubation and increase the postoperative pulmonary complications.

In our study, there was no significant difference on hemodynamic parameters between two groups, such as: SBP, DBP, HR and CVP. It was suggested that IRV (I:E = 1:2) applying PEEP didn't hamper venous return with possible consequent hemodynamic derangement. It is consistent with the previous statement that increasing the percentage of inspiratory time had no demonstrable changes in hemodynamic during mechanical ventilation [16].

In this experiment, the IL-1β, IL-6 and IL-8 of BALF were increased significantly at 45 min of one-lung ventilation in both groups, and levels of IL-1β, IL-6 and IL-8 in IRV group were significantly lower compared with the control group. One-lung ventilation caused inflammatory response possibly because inflammation factors were activated and released. Inflammatory factors play an important role in the stress response, including IL-1β, IL-6 and IL-8, which are important pro-inflammatory factor [17]. In the mechanical lung injury, IL-6 is one of the most important inflammatory mediators, its concentration was positively correlated with the degree of lung injury [18]. Neutrophils play a central role in the inflammatory response. Upon infection and/or tissue damage, the neutrophils must first adhere to endothelium in response to chemokines presented at the endothelial interface and then migrate out of the microvasculature by following other chemokines secreted from nearby macrophages, mast cells, and other serosal cells. The neutrophils would then follow a series of end target chemoattractants such as IL-8 or LTB4 to the final site of infection [19]. In addition, damaged-molecular-patterns (DAMPs) are molecules that have a physiological role inside the cell, but acquire additional functions when they are exposed to the extracellular environment: they alert the body about danger, stimulate an inflammatory response, and

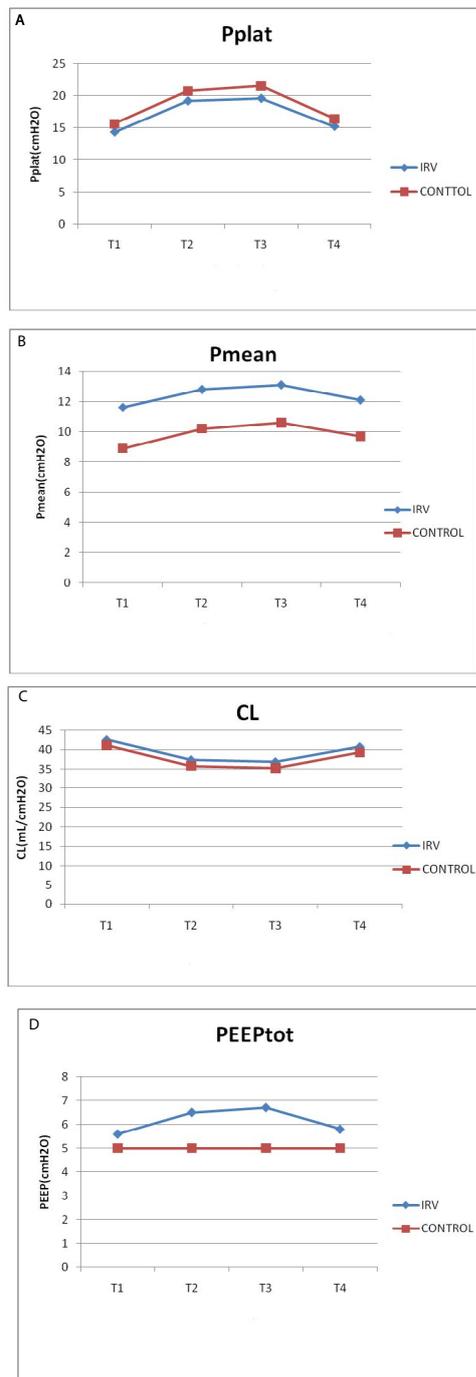


Figure 1: Comparison of respiratory parameters of patients in both groups. A) Comparison of Pplat at different time in two groups ($P < 0.001$). X axis-time point, Y axis-plateau pressures. B) Comparison of mean airway pressures different time ($P < 0.001$). X axis-time point, Y axis-mean airway pressure. C) Comparison of CL at different time in two groups ($P < 0.05$). X axis-time point, Y axis-dynamic compliance. D) Comparison of total PEEP at different time ($P < 0.05$). X axis-time point, Y axis-total PEEP. T0: At 5 min before anesthesia induction; T1: At 5 min after bronchial intubation; T2: At initiate of OLV; T3: At 45 min after OLV; T4: The end of surgery.

finally promote the regeneration process. Beside their passive release by dead cells, some DAMPs can be secreted or exposed by living cells undergoing a life-threatening stress [20]. DAMPs could target the cytokines synthesis during hypoxic condition. They played a role in the inflammatory response, so that the release of the IL-1 β , IL-6 and

IL-8 would increase in lung tissue. The IL-1 β , IL-6 and IL-8 were large released on the condition of hypoxia or lung tension. Studies suggested that inverse ratio ventilation could alleviate the inflammatory response.

The typical forms of lung injury are as following: volutrauma, barotraumas, atelectrauma and biological lung injury [21]. In this

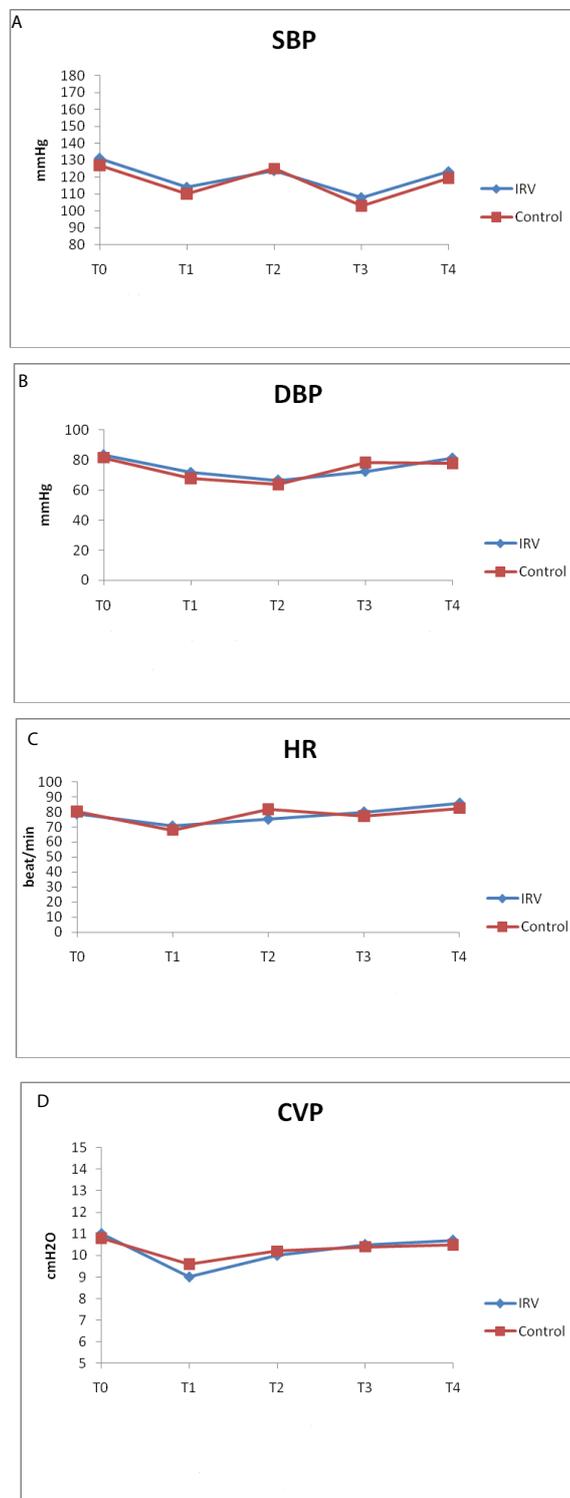


Figure 2: Comparison of hemodynamic parameters in both groups. A) Comparison of systolic pressure in two groups ($p > 0.05$), X axis-time, Y axis-systolic pressure in mmHg. B) Comparison of diastolic blood pressure in two groups ($p > 0.05$), X axis-time, Y axis- diastolic blood pressure. C) Comparison of diastolic heart rates in two groups ($p > 0.05$), X axis-time, Y axis- heart rate. D) Comparison of CVP in two groups ($p > 0.05$), X axis-time, Y CVP. T0: At 5 min before anesthesia induction; T1: At 5 min after bronchial intubation; T2: At initiate of OLV; T3: At 45 min after OLV; T4: The end of surgery.

study, some degree of inflammation was already present probably due to surgery, trauma, anesthesia and injurious mechanical ventilation, and so on. Inverse ratio ventilation could low the P_{plat} , increase P_{mean} and alleviate the inflammatory response. It maybe alleviate acute lung injury. Using inverse ratio ventilation, we obtained good ventilation and prevented lung injury with PEEP. It is consistent with the protective ventilation strategy.

IRV is different from the normal ratio ventilation: there may be some shortcomings or potential risks, whether will cause respiratory dysfunction or other adverse effects remain to be studied further. Moreover, the other limitation of this study is that anesthesiologist is not blinded to ventilation strategy.

To sum up, IRV applying PEEP can improve hypoxemia, promote oxygenation and increase dynamic compliance of respiratory system. Therefore, when applying low external PEEP, IRV is considered to be superior to conventional ratio ventilation in terms of gas exchange and respiratory mechanics in patients during OLV.

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Authorship and Contributorship

Zhang WP collected the data and performed the research and Zhu SM performed the research.

Ethics

The study was approved by the Ethics Committee of Hospital.

Conflict of Interest

There are no conflicts of interest in connection with this article.

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