Int J Clin Exp Med 2016;9(11):21732-21739
www.ijcem.com /ISSN:1940-5901/IJCEM0029301

Original Article

The effects of volume control inverse ratio ventilation with PEEP on respiratory function and inflammatory cytokines in patients during one-lung ventilation

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Received March 25, 2016; Accepted September 7, 2016; Epub November 15, 2016; Published November 30, 2016

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 thoracoctomy 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 cmH_2O. Arterial blood was collected respectively to analyze blood gas before and during OLV. Meanwhile, hemodynamic and respiratory mechanics were monitored. The concentrations of interleukin (IL)-1β, 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 (PaO_2), mean airway pressure (Pmean) and dynamic compliance (CL) were significantly higher in IRV group during OLV ($P<0.05$). However, plateau pressure (Pplat) and levels of IL-1β, IL-6 and IL-8 in BALF were lower in IRV group than those in control group ($P<0.05$). Conclusions: IRV (I:E=2:1) applying PEEP could improve hypoxemia, promote oxygenation, and improve CL of respiratory system, moreover reduce Pplat 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

It is reported that the incidence of hypoxemia during one-lung ventilation (OLV) is from 5% to 10% [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). Beside, the previous study proved that PEEP could improve oxygenation [8, 9], and IRV could decrease peak airway pressure and plateau airway pressure, 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 lung lobectomy during one-lung ventilation, is superior to conventional ventilation with PEEP. The primary endpoint was that IRV (I:E=2:1) applying external PEEP would reduced Pplat.

Materials & methods

This study was approved by the Hospital Ethics Committee of Jiaxing 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 , weight 51-75 kg and maximal ventilation volume (MMV)>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 (SpO_2) and central venous pressure (CVP) were applied and venous access was established. Anesthesia was induced with intravenous propofol 2 mg/kg, fentanyl 5 ug/kg and rocuronium 0.6 mg/kg, then bronchial intubation was performed using direct laryngoscope. Anesthesia was maintained with propofol 6-10 $mg.kg^{-1}.h^{-1}$ and remifentanil 0.4-1 $ug.kg^{-1}.min^{-1}$ to keep the bispectrail index (BIS) value between 40 to 55 (Model A2000, Aspect Medical Systems Inc., Natick, MA, 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 (Type TOF-Watch SX, Organon, Holland). Continuous infusion of rocuronium was performed to maintain stable neuromuscular block.

The trachea was intubated using a double-lumen tube (37 F for males and 39 F 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. 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 cmH_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 switched and both lungs were re-expanded by hand bagging in all patients.

Mean airway pressure (Pmean), plateau airway pressure (Pplat), total PEEP (PEEPtot), 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 ug/kg was administered for pain control at 30 min before the end of surgery. Postoperative complications were observed, such as discharge 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 $ml.kg^{-1}.h^{-1}$.

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, Pmean, Pplat, PEEPtot 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

Table 1. Data of patients in both groups

index	IRV	control	*P* value
Age (year)	56.0 ± 13.1	54.3 ± 12.7	0.519
Weight (kg)	64.8 ± 5.2	63.2 ± 4.8	0.637
Gender (male/female)	17/13	16/14	0.067
MMV (L/min)	85.2 ± 11.8	87.4 ± 13.2	0.501
Duration of OLV (min)	68.9 ± 12.6	73.1 ± 16.1	0.269
Duration of operation (min)	116.5 ± 26.8	123.2 ± 31.6	0.382
PACU discharge time (min)	57.2 ± 14.6	53.3 ± 13.2	0.286
Intra-operative hypoxemia	1	3	0.789

Data are mean ± SD or number. MMV: maximal ventilation volume, PACU: post anesthesia careunit.

Table 2. Arterial blood gas in both groups

	IRV	Control	*P* value
Arterial blood gas at T1 point			
pH	7.37 ± 0.04	7.36 ± 0.02	0.167
PaO_2 (mmHg)	89.5 ± 7.8	91.6 ± 8.7	0.199
$PaCO_2$ (mmHg)	35.2 ± 2.8	34.5 ± 2.5	0.247
SaO_2 (%)	99.82 ± 0.13	99.79 ± 0.17	0.274
$ScvO_2$ (%)	68.7±2.6	69.4 ± 2.8	0.297
Arterial blood gas at T3 point			
pH	7.32 ± 0.06	7.34 ± 0.07	0.180
PaO_2 (mmHg)	232.7 ± 45.6	196.5 ± 35.5	0.004*
$PaCO_2$ (mmHg)	38.65 ± 5.4	36.87 ± 3.9	0.240
SaO_2 (%)	99.68 ± 1.8	99.56 ± 1.6	0.754
$ScvO_2$ (%)	77.9 ± 3.1	78.3 ± 3.4	0.796

Data are mean ± SD, *means statistically significant ($P<0.05$). T1: at 5 min after bronchialintubation, T3: at 45 min of one-lung ventilation. $ScvO_2$: oxygen saturation of central venous blood.

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

	IRV	Control	*P* value
At T1 point			
IL-1β (ng/L)	76.5 ± 14.5	72.8 ± 12.4	0.296
IL-6 (ng/L)	118.6 ± 30.6	112.4 ± 23.1	0.382
IL-8 (ng/L)	83.6 ± 17.9	80.4 ± 15.8	0.468
At T3 point			
IL-1β (ng/L)	91.6 ± 21.2	106.7 ± 26.7	0.021*
IL-6 (ng/L)	149.3 ± 34.6	177.8 ± 40.3	0.006*
IL-8 (ng/L)	102.4 ± 22.4	117.7 ± 25.6	0.019*

Data are mean ± standard deviation. Compared with the control group, **p* means statisticallysignificant ($P<0.05$). TI: at the initiate of mechanical ventilation, T3: at 45 min of one-lungventilation. IL: interleukin.

T3 point. At T1 and T3 point, we collected bronchoalveolar lavage fluid performed by infilliting 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°C, saved for assay at -70°C. IL-1β, 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

Sample size based on a previous trial test. The main variable in the study, Pplat 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. Descriptive statics and compliance with normal distribution was examined with one-sample Kolmogorov-Smirnov test. Comparisons between groups were evaluated using Student *t* test for parametric data and Mann-Whitney *U*-test for nonparametric data. Categorical variables were analyzed by the Chi-square test. Data were presented as mean ± standard deviation. Significance was considered as *P* value<0.05. Data analysis was performed using the statistical software package SPSS 19.0 (SPSS Inc., Chicago, USA).

Results

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

The P mean, PEEPtot 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 the two groups ($P<0.05$), but Pplat was lower in IRV group (**Figure 3**), there was statistical significance ($P<0.05$). Hemodynamic monitoring

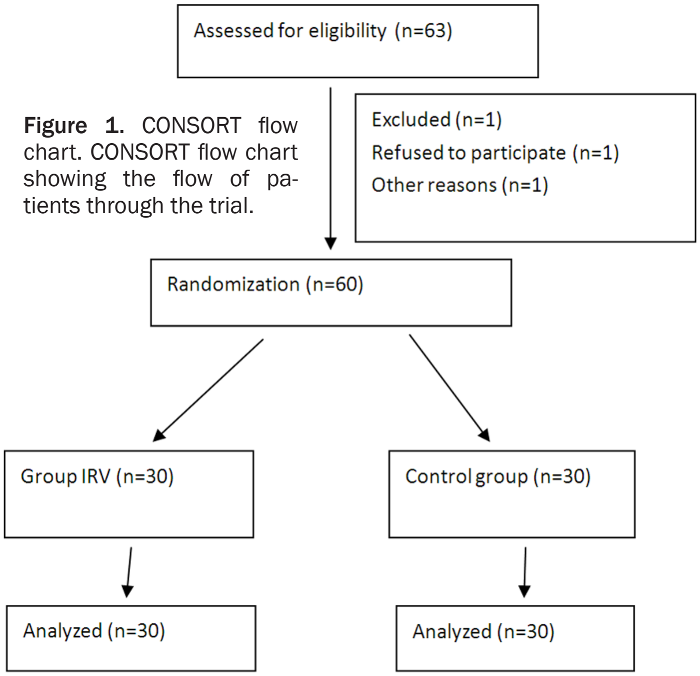

Figure 1. CONSORT flow chart. CONSORT flow chart showing the flow of patients through the trial.

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-1β were lower in IRV group than those in the control group at T3, there was statistically significant between the two 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 the two groups ($P<0.05$). There was no significance in the incidence of intraoperative hypoxemia, time to extutation and discharge time in PACU between the 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. It 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. However 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 Pplat, higher Pmean, PEEP total and CL were observed in IRV group compared with the control group. Lower Pplat in IRV group was possibly because of the longer inspiratory time or slow inspiratory flow, and higher Pmean was achieved by moderate prolongation of I:E ratio [11]. Prolonging inspiratory time resulted in increases in Pmean and decreases in Ppeak or Pplat 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 in IRV group were possibly as following: firstly, Pmean 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 factor probably to improve oxygenation, which facilitated the mixing of gas, made collapse alveoli reopen and prevented atelectasis.

IRV would increase the Pmean, recruit atelectatic alveoli, reduce intrapulmonary shunt, improve ventilation-perfusion mismatch and decrease dead space ventilation [12]. In IRV group, prolonged inspiratory time allows enough time to gas exchange. Meanwhile, as expiratory time was shorter, IRV 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. $PaCO_2$ 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 CO_2 [15], which was agreement with the

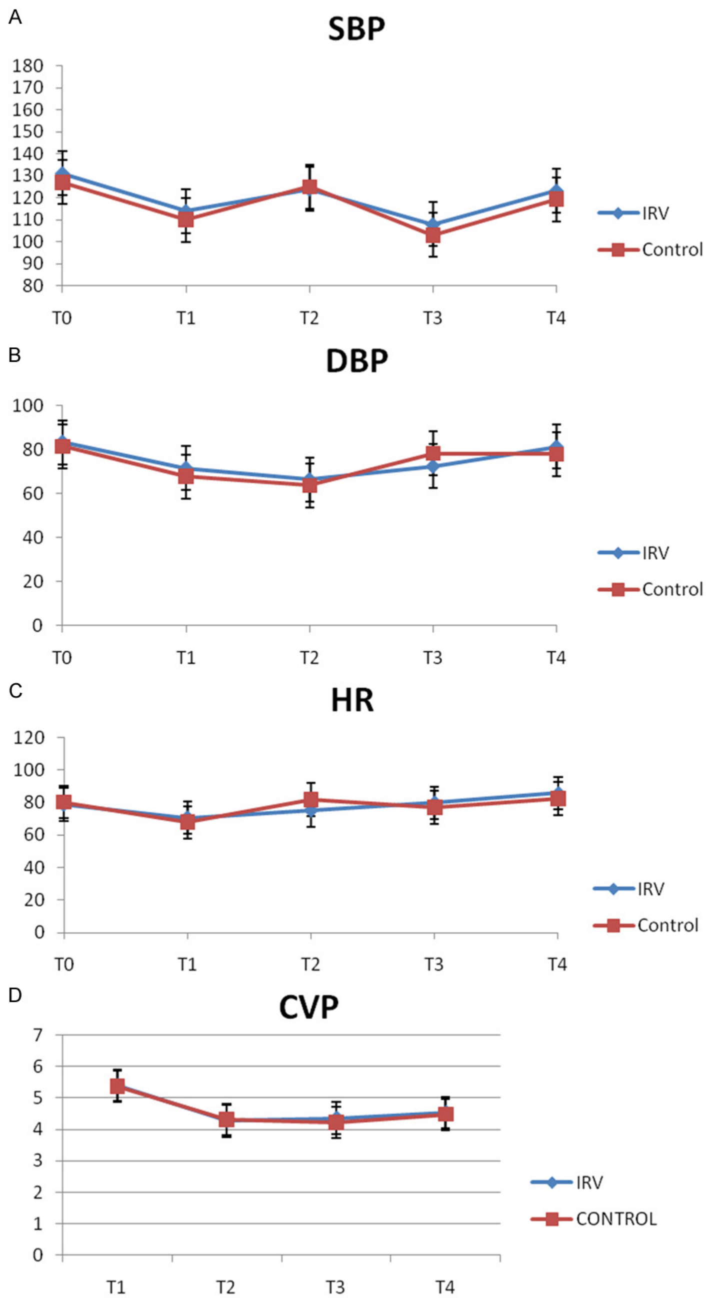

Figure 2. Comparison of hemodynamic parameters in both groups. Legend: SBP: arterial diastolic blood pressure, DBP: arterial diastolic blood pressure, HR: heart rate, CVP: central venous pressure. Comparison of SBP, DBP, HR and CVP between the two groups, there was no statistical significance (*P*>0.05). T0: at 5 min before anesthesia induction, T1: 5 min after bronchial intubation, T2: the initiate of OLV, T3: 45 min of OLV, T4: the end of surgery. A. Comparison of systolic blood time in both groups (*p*>0.05). X axis-time point, Y axis-systolic blood pressure in mmHg. B. Comparison of diastolic blood pressure in both groups (*p*>0.05). X axis-time point, Y axis-diastolic blood pressure in mmHg. C. Comparison of Heart rate in both groups (*p*>0.05). X axis-time point, Y axis-heart rate in beat per min. D. Comparison of central venous pressure in both groups (*p*>0.05). X axis-time point, Y axis-central venous in cmH_2O.

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 the 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 was 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 levels of IL-1β, IL-6 and IL-8 in BALF were increased significantly at 45 min of one-lung ventilation in both groups, and the levels of IL-1β, IL-6 and IL-8 in IRV group were significantly lower than those in the control group. OLV caused inflammatory response in thoracic surgery 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 ventilator-induced lung injury, IL-6 is one of the most important inflammatory mediators, its concentration was positively correlated with the degree of lung injury [18], and 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 mac-

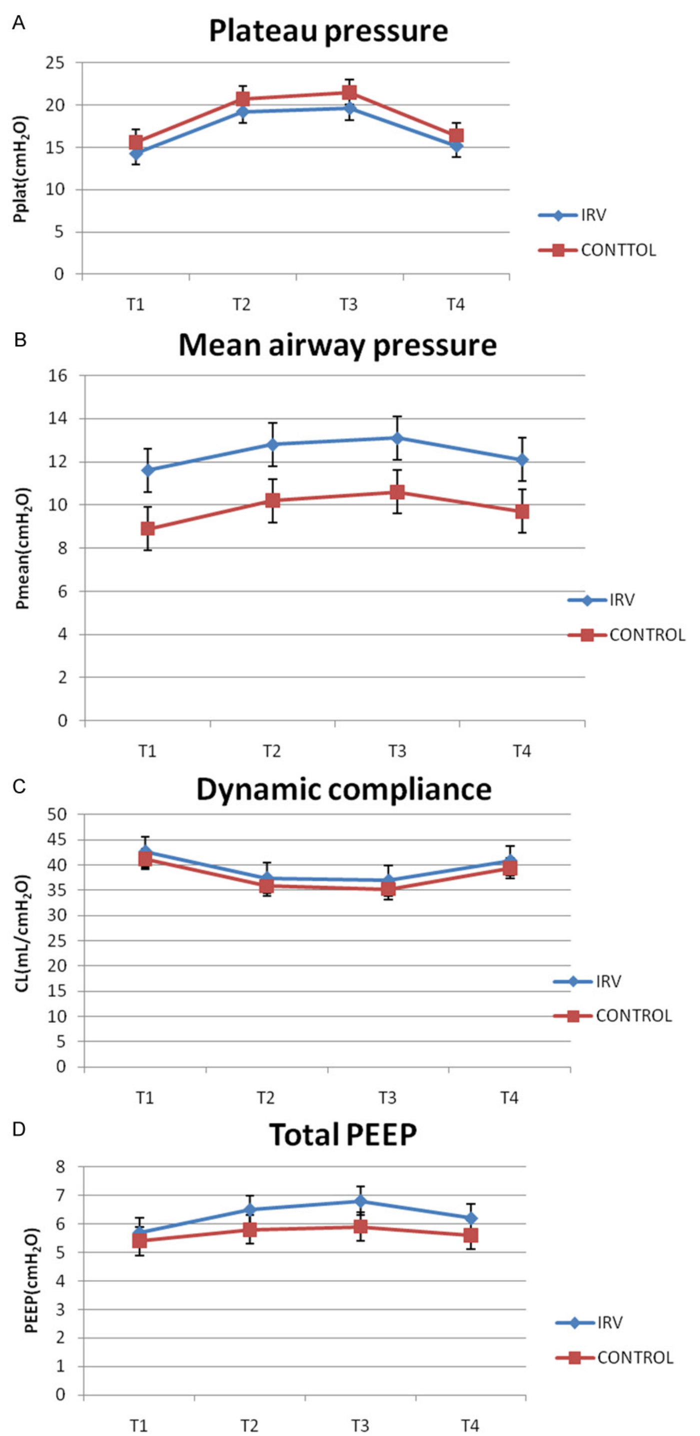

Figure 3. Comparison of Respiratory parameters of patients in both groups. Legend: Comparison of the Pplat, Pmean, PEEPtot and CL at T1, T2, T3 and T4 in the both groups, there was statistically significant between the two groups ($P<0.05$). Mean airway pressure (Pmean), plateau airway pressure (Pplat), total PEEP (PEEPtot), dynamic compliance of respiratory system (CL). T1: at 5 min after bronchial intubation, T2: the initiate of OLV, T3: 45 min of OLV, T4: the end of surgery. A. Comparison of plateau pressure at diffrent time in two groups ($p>0.05$). X axis-time point, Y axis-plateau pressure. B. Comparison of mean airway pressures at diffrent time ($p>0.05$). X axis-time point, Y axis-mean airway pressure. C. Comparison of dynamic compliance at diffrent time in two groups ($p>0.05$). X axis-time point, Y axis-dynamic compliance. D. Comparison of total PEEP at diffrent time ($p>0.05$). X axis-time point, Y axis-total PEEP.

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

The typical forms of lung injury are as following: volutrauma, barotraumas, atelectrauma and biological lung injury [21]. In this study, some inflammatory response had been already present probably due to surgery, trauma, anesthesia and injurious mechanical ventilation, and so on. IRV could low the Pplat, increase Pmean and alleviate the inflammatory response. It maybe alleviate acute lung injury. Applying IRV, we obtained good ventilation and prevented lung injury with PEEP. It was 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 could 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.

Acknowledgements

This work was supported by Zhejiang clinical medical research foundation (2015-ZYC-A71).

Disclosure of conflict of interest

None.

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References

[1] Karzai W, Schwwarzkopf K. Hypoxermia during one-lung ventilation: prediction, prevention, and treatment. Anesthesiology 2009; 110: 1402-1411.

[2] Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology 2006; 105: 14-8.

[3] Mercat A, Titiriga M, Anguel N, Richard C, Teboul JL. Inverse ratio ventilation (I/E=2/1) in acute respiratory distress syndrome. Am J Respir Crit Care Med 1997; 155: 1637-42.

[4] Huang CC, Shih MJ, Chang YC, Tsao TC, Hsu KH. Effects of inverse ratio ventilation versus positive end-expiratory pressure on gas exchange and gastric intramucosal PaCO(2) and pH under constant mean airway pressure in acute respiratory distress syndrome. Anesthesiology 2001; 95: 1182-8.

[5] Gurevitch MJ, Van Dyke J, Young ES, Jackson K. Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome: Treatment with inverse ratio ventilation. Chest 1986; 89: 211-3.

[6] Talab HF, Zabani IA, Abdelrahman HS, Bukhari WL, Mamoun I, Ashour MA. Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. Anesth Analg 2009; 109: 1511-16.

[7] Sari A, Yamashita S, Toriumi T, Nakashima K, Kawata R, Kunihiro M, Yonei A. The effects of inversed ratio ventilation (IRV)on arterial oxygenation during mechanical ventilation in patients with acute respiratory failure. Resuscitation 1991; 22: 93-101.

[8] Maracaja-Neto LF, Vercosa N, Roncally AC, Giannella A, Bozza FA, Lessa MA. Beneficial effects of high positive end-expiratory pressure in lung respiratory mechanics during laparoscopic surgery. Acta Anaesthesiol Scand 2009; 53: 210-7.

[9] Karsten J, Luepschen H, Grossherr M, Bruch HP, Leonhardt S, Gehring H. Effect of PEEP on regional ventilation during laparoscopic surgery monitored by electrical impedance tomography. Acta Anaesthesiol Scand 2011; 55: 878-86.

[10] Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995; 7: 89-91.

[11] Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. Lancet 2003; 361: 332-40.

[12] Pesenti A, Marcolin R, Prato P, Borelli M, Riboni A, Gattinoni L. Mean airway pressure vs. positive end-expiratory pressure during mechanical ventilation. Crit Care Med 1985; 13: 34-7.

[13] Andersson LE, Baath M, Thorne A, Aspelin P, Odeberg-Wernerman S. Effect of carbon dioxide pneumoperitoneum on development of atelectasis during anesthesia, examined by spiral computed tomography. Anesthesiology 2005; 102: 293-9.

[14] Ludwigs U, Klingstedt C, Baehrendtz S, Hedenstierna G. A comparison of pressure- and volume-controlled ventilation at different inspiratory to expiratory ratios. Acta Anaesthesiol Scand 1997; 41: 71-7.

[15] Sinha M, Chiplonkar S. Ghanshani R. Pressure-controlled inverse ratio ventilation using laryngeal mask airway in gynecological laparoscopy. J Anaesthesiol Clin Pharmacol 2012; 28: 330-3.

[16] Manthous CA, Lewis TH. Increased blood pressure during inverse ratio ventilation in two patients with adult respiratory distress syndrome. Chest 1993; 104: 1625-7.

[17] Slutsky AS, Imai Y. Ventilator-induced lung injury, cytokines, PEEP, and mortality: implication for practice and for clinical trials. Intensive Care Med 2003; 29: 1218-1221.

[18] Bouqren A, Dehoux MS, Seta N, Ostinelli J, Venembre P, Crestani B. Compartmentalized IL-8 and elastase release within the human lung in unilateral pneumonia. Am J Respir Crit Care Med 1996; 153: 336-342.
[19] Heit B, Tavener S, Raharjo E, Kubes P. An intracellular signaling hierarchy determines direction of migration in opposing chemotactic gradients. J Cell Biol 2002; 159: 91-102.
[20] Vénéreau E, Ceriotti C and Bianchi ME. DAMPs from Cell Death to New Life. Front Immunol 2015; 6: 422.
[21] Manicone AM. Role of the pulmonary epithelium and inflammatory signals in acute lung injury. Expert Rev Clin Immunol 2009; 5: 63-75.