

Clinical Research Paper

Effects of the lung protective ventilatory strategy on proinflammatory cytokine release during one-lung ventilation

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Key words: lung protective ventilation, esophageal neoplasms/surgery, one-lung ventilation, proinflammatory cytokine

Background and Objective: A prolonged period of one-lung ventilation (OLV) is required during thoracic surgery and this may activate cytokine release and cause lung inflammatory response. The lung protective ventilatory strategy has reduced lung and systemic cytokine release and achieved remarkable curative effect in patients with acute respiratory distress syndrome (ARDS). This study was to investigate the effect of the lung protective ventilatory strategy on proinflammatory cytokine release during OLV in patients underwent thoracic surgery. **Methods:** Forty patients underwent esophagectomy were randomly divided into conventional ventilation (CV) group ($n = 20$) and protective ventilation (PV) group ($n = 20$). In CV group, all patients received two-lung ventilation (TLV) and OLV with a tidal volume (V_T) of 10 ml/kg and an inspiration/expiration ratio (I/E) of 1:1.5. In PV group, all patients received TLV with a V_T of 10 ml/kg and an I/E ratio of 1:1.5, and received OLV with a V_T of 5–6 ml/kg and an I/E ratio of 1:1, along with positive end-expiratory pressure (PEEP) preset at 3–5 cm H_2O . Blood samples of 3 ml were extracted at three time courses, which were after tracheal intubation (T1), 120 min after OLV (T2) and 24 h after operation (T3), to analyze concentrations of interleukin (IL) 6 and IL8 in the two groups. Values of airway peak pressure (Ppeak), airway plateau pressure (Pplat), and airway resistance (Raw) were also recorded using side stream spirometry. **Results:** In CV group, concentrations of IL6 and IL8 at T2 [(269.4 $\pm$ 57.2) ng/L, (180.8 $\pm$ 35.0) ng/L] and T3 [(335.8 $\pm$ 98.7) ng/L, (178.5 $\pm$ 18.3) ng/L] were significantly increased as compared with those at T1 [(17.0 $\pm$ 5.4) ng/L, (18.2 $\pm$ 2.8) ng/L] ($p < 0.05$). In PV group, concentrations of IL-6 and IL-8 at T2 [(209.3 $\pm$ 55.7) ng/L, (115.3 $\pm$ 71.5) ng/L] and T3 [(278.2 $\pm$ 100.8) ng/L, (124.2 $\pm$ 40.1) ng/L] were significantly increased as compared

with those at T1 [(20.0 $\pm$ 7.1) ng/L, (15.3 $\pm$ 3.6) ng/L] ($p < 0.05$). Concentrations of IL6 and IL8 at T2 and T3 were significantly higher in CV group than in PV group ($p < 0.05$). Ppeak, Pplat and Raw at T2 were significantly higher in CV group [(33.6 $\pm$ 4.6) cm H_2O , (21.5 $\pm$ 3.1) cm H_2O , (26.3 $\pm$ 2.1) cm H_2O .L $^{-1}$.s $^{-1}$] than in PV group [(26.7 $\pm$ 3.5) cm H_2O , (12.4 $\pm$ 2.1) cm H_2O , (18.3 $\pm$ 2.3) cm H_2O .L $^{-1}$.s $^{-1}$] ($p < 0.05$). **Conclusion:** Concentrations of IL6 and IL8 are increased during and after OLV in thoracic surgery. The lung protective ventilatory strategy can reduce the airway pressure and airway resistance during OLV, decrease the release of IL6 and IL8, and inhibit lung inflammatory responses during OLV and postoperatively.

During mechanical ventilation, a high tidal volume or high airway pressure may result in massive release of proinflammatory cytokines, induce or aggravate lung injuries, and even lead to postoperative pulmonary complications.^{1,2} A prolonged period of one-lung ventilation (OLV) is required during thoracic surgery. It has been reported that OLV is accompanied by a substantial increase of proinflammatory cytokine release into the plasma, resulting in systemic and pulmonary infection. This phenomenon is likely to be caused by a relatively high tidal volume and airway pressure during OLV, which results in extensive lung inflation and deflation.²⁻⁵

Remarkable therapeutic effects have been achieved by adopting the strategy of small tidal volume, low airway pressure and low positive end expiratory pressure (PEEP) ventilation. This strategy minimizes alveolar damage, reduces proinflammatory cytokine release and improves alveolar oxygenation.⁶ Whether lung protective ventilation can reduce proinflammatory cytokine release and alleviate inflammatory response in normal lung tissues, particularly in individualized OLV still remains unclear. This study was to explore the effects of pulmonary protective ventilation on proinflammatory cytokine release during OLV in patients with esophageal carcinoma underwent thoracic surgery.

Data and Methods

Clinical data. Forty patients with esophageal carcinoma from the Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, from May 2005 to February 2006, were chosen to perform radical surgery for esophageal carcinoma under general anesthesia. There were 31 males and nine females, ranging in age from 41–65 years, with a median age of 55 years. All patients had no history of

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Submitted: 07/08/07; Revised: 01/30/08; Accepted: 03/19/08

This paper was translated into English from its original publication in Chinese. Translated by: Beijing Xinglin Meditrans Center and Hua He on 05/21/08.

The original Chinese version of this paper is published in: *Ai Zheng* (Chinese Journal of Cancer), 27(8); <http://www.cjcsysu.cn/cn/article.asp?id=13991>

Previously published online as a *Chinese Journal of Cancer* E-publication: <http://www.landesbioscience.com/journals/cjc/article/6529>

hypertension and cardiovascular disease; their tests of lung function were normal; and they had no infections of the respiratory tract or pulmonary before surgery. Patients were randomly divided into conventional ventilation group (CV group) and protective ventilation group (PV group), 20 cases in each group.

Anesthetic procedure. Anesthetic induction in both groups was performed as below: after intravenous injection of 0.1 mg/kg midazolam, 4 µg/kg fentanyl, 1 mg/kg propofol, 0.15 mg/kg vecuronium bromide for 3 min, a double channel catheter was inserted into the patient's trachea and successful insertion was confirmed by auscultation and fiberbronchoscopy (Pentax FI-10P2, Pentax Inc., Japan). Respiration was monitored by the Ohmeda Aestiva 7100 anesthesia machine. For maintenance of anesthesia, continuous pumping of 0.08–0.15 µg·min⁻¹·kg⁻¹ remifentanyl, 3–4 mg·kg⁻¹·h⁻¹ propofol, 0.06–0.08 mg·kg⁻¹·h⁻¹ vecuronium bromide was used in both groups. The bispectral index (BIS) value was maintained at around 50. Inhaled anesthesia was not used in both groups. In CV group, all patients received two-lung ventilation (TLV) and OLV with a tidal volume (V_T) of 10 ml/kg and an inspiration/expiration ratio (I/E) of 1:1.5; respiratory rates were adjusted to keep P_{ET}CO₂ between 4–4.7 kPa (1 kPa = 7.5 mmHg). In PV group, all patients received TLV with a V_T of 10 ml/kg and an I/E ratio of 1:1.5, and received OLV with a V_T of 5–6 ml/kg and an I/E ratio of 1:1, plus positive end-expiratory pressure (PEEP) preset at 3–5 cmH₂O; respiratory rates were adjusted to keep P_{ET}CO₂ within normal ranges. In both groups, internal jugular vein and radial artery catheterizations were performed to monitor blood pressure and collect samples. GE Solar 8000 multifunctional patient monitors (USA) were used to monitor patients' vital signs; airflow monitor was used to monitor respiratory mechanics: V_T, respiration rate (RR), PEEP, airway peak pressure (Ppeak), airway plateau pressure (Pplat), airway resistance (Raw), and dynamic compliance (Cdyn).

Event observation. Venous samples (3 mL) were extracted at three time courses, which were after tracheal intubation (T1), 120 min after OLV (T2) and 24 h after operation (T3). Samples were centrifuged at 3000 r/min for 10 min, and suspensions were collected and stored under -70°C for future use. Meanwhile, arterial samples were also collected for blood gas analysis using a bedside I-STAT blood gas analyzer. The index of oxygenation (OI) was calculated as OI = PaO₂/FiO₂. Concentrations of IL6 and IL8 were determined by ELISA. The ELISA kit was provided by Shenzhen Jingmei Co., Ltd. The lowest determination concentration was 10 ng/L.

Statistical analysis. Results were analyzed using SPSS11.5 statistical software. Quantitative results were expressed as mean ± standard deviation (SD). Comparisons of data within the same group were calculated using single factor analysis of variance; while comparisons of data between different groups were calculated using group t-test. Comparisons of qualitative data were calculated using chi-square test (one-sided test), where p < 0.05 was considered as significantly different.

Results

Comparisons of general and surgical conditions between CV and PV groups. During OLV, the tidal volume differed significantly between group CV and PV (p = 0.023) (Table 1); while the other indicators showed no significant difference (p > 0.05).

Changes in proinflammatory cytokine release in CV and PV groups. Plasma concentrations of IL6 and IL8 were significantly

Table 1 **Clinical and intraoperative data of patients in conventional ventilation group (CV) and protective ventilation group (PV)**

Item	PV group	CV group	p value
Gender (Male/Female)	15/5	16/4	0.472
Median age (yrs)	55	54	0.421
Body weight (kg)	55.3 ± 11.8	58.4 ± 15.7	0.460
Open chest surgery (Left/Right)	16/4	15/5	0.432
Surgery duration (min)	230 ± 31	241 ± 32	0.431
Mechanical ventilation duration (min)	260 ± 54	256 ± 43	0.423
One lung ventilation duration (min)	142 ± 21	154 ± 32	0.321
Tidal volume (ml/kg, OLV)	5.4 ± 0.2	9.4 ± 1.1	0.023
Respiratory rate (times/min)	13 ± 3.2	11 ± 2.1	0.323

Table 2 **Comparisons of concentrations of IL6 and IL8 between CV group and PV group at different time course**

Item	Group	T1	T2	T3
IL-6 (ng/L)	PV	20.0 ± 7.1	209.3 ± 55.7 ^a	278.2 ± 100.8 ^a
	CV	17.0 ± 5.4	269.4 ± 57.2 ^{a,b}	335.8 ± 98.7 ^{a,b}
IL-8 (ng/L)	PV	15.3 ± 3.6	115.3 ± 71.5 ^a	124.2 ± 40.1 ^a
	CV	18.2 ± 2.8	180.8 ± 35 ^{a,b}	178.5 ± 18.3 ^{a,b}

T1: after tracheal intubation; T2: 120 min after one-lung ventilation; T3: 24 h after operation. ^ap < 0.05, vs. T1; ^bp < 0.05, vs. PV group.

Table 3 **Comparisons of respiratory variables and oxygenation indexes between CV group and PV group**

Item	Group	T1	T2	T3
Ppeak (cmH ₂ O)	CV	17.3 ± 1.8	33.6 ± 4.6	-
	PV	16.9 ± 2.1	26.7 ± 3.5 ^a	-
Pplat (cmH ₂ O)	CV	15.2 ± 2.9	21.5 ± 3.1	-
	PV	15.4 ± 2.7	12.4 ± 2.1 ^a	-
Raw (cmH ₂ O·L ⁻¹ ·s ⁻¹)	CV	18.1 ± 1.8	26.3 ± 2.1	-
	PV	17.9 ± 1.7	18.3 ± 2.3 ^a	-
Cdyn (mL/cmH ₂ O)	CV	43.6 ± 7.9	48.8 ± 8.9	-
	PV	45.6 ± 8.9	40.5 ± 6.3 ^a	-
OI (mmHg)	CV	450 ± 60	360 ± 54	310 ± 34
	PV	460 ± 55	401 ± 56 ^a	360 ± 32 ^a

Ppeak, airway peak pressure; Pplat, airway plateau pressure; Raw, airway resistance; Cdyn, dynamic compliance; OI, oxygenation index. T1: after tracheal intubation; T2: 120 min after one-lung ventilation; T3: 24 h after operation. ^ap < 0.05, vs. CV group.

higher at T2 and T3 than at T1 in both groups, and were significantly higher in CV group than in PV group (p < 0.05) (Table 2).

Comparisons of respiratory mechanics between CV and PV groups. Levels of Ppeak, Pplat, Raw and Cdyn at T2 were significantly higher in CV group than in PV group (p < 0.05). Oxygenation index (OI) levels at T2 and T3 in PV group were significantly higher than those in CV group (p < 0.05) (Table 3). One day after operation, bedside chest X-rays found two (2/20) and three (3/20) cases of

suspected atelectasis in CV group and PV group respectively, located at the left lower lobe of the lung (the non-ventilated side). The difference between the two groups were not statistically significant ($p = 0.8$). No abnormalities were observed on re-examination of chest X-rays two days later after sputum suction and improvement of the drainage of the pleural space.

Discussion

Mechanical ventilation is a commonly implemented technique used in clinical anesthesia and intensive care treatments. However, pulmonary injuries caused by mechanical ventilation have increasingly drawn our attention. Animal experiments have confirmed that, when mechanical tractions are applied on alveolar epithelial cells and vascular endothelial cells, transcriptions and expressions of some genes are subsequently activated, resulting in increased transcription of IL6, IL8 and other proinflammatory cytokines. These cytokines play important roles in inducing lung injuries.^{2,7} Studying on these cytokines may help to understand, as well as prevent mechanical ventilation-associated pulmonary injuries. During OLV, prevention of hypoxia is the primary concern, therefore a tidal volume applied for TLV is used. Some studies claim that this strategy produces a relatively high tidal volume during OLV, coupled with the effect of lateral recumbent position, resulting in a significant rise of airway pressure.^{4,8} We found significant differences in respiratory mechanics and proinflammatory cytokines levels during OLV between CV and PV groups. Ppeak, Pplat, Raw, as well as levels of IL6 and IL8 at 120 min during OLV were significantly lower in PV group than in CV group, consistent with the above mentioned studies. These results suggest that protective ventilation may reduce alveolar irritation caused by mechanical ventilation, and subsequently reduce the release of proinflammatory cytokines through increasing respiratory compliance and lowering ventilation pressure and airway resistance.

IL6 is released by various cells, such as alveolar macrophages, endothelial cells and so on, when they are stimulated, such as by traction. A sharp rise of IL6 level can be related to acute phase response, which leads to massive activation of proinflammatory cytokines. Therefore, IL6 is highly associated with pulmonary injuries and complications.⁹ IL8 is also produced by alveolar macrophages. As a neutrophil chemotactic factor, IL8 can induce neutrophil aggregation and degranulation, cause respiratory burst, as well as produce elastase, thus lead to pulmonary injuries. IL8 level is also highly associated with pulmonary injuries.¹⁰ We expect that deduced levels of IL6 and IL8 may effectively prevent pulmonary complications. Abe et al.¹¹ discovered that the level of IL6 was significantly increased during perioperative period for esophageal carcinoma, suggesting an association between the inflammatory response produced by systemic and pulmonary tissues with mechanical ventilation and surgery stimulation. Multiple researches have revealed that,^{12,13} V_T and Ppeak are the major risk factors which could induce pulmonary inflammatory response. In our study, a significant increase of IL6 and IL8 at T2 appeared in both CV and PV group, which lasted for one day after surgery, accompanied with progressive reduction of OI, implying appearance of pulmonary inflammatory response as well as possible pulmonary injuries. Our findings were in accordance with above mentioned studies. However, the extent of increase was significantly lower in PV group than in CV group, further confirming the hazards of large V_T and high Ppeak, which may induce the “first hit”, even

the “second or third hit” to alveolar.⁸ The strategy of protective ventilation is to reduce the tidal volume and lower airway pressure, so as to avoid excessive lung inflation and deflation, reduce shear stress and so on.^{6,13} Currently, the tidal volume set for patients with normal lung function during OLV is yet to be confirmed. It is also suggested that “small tidal volume” is actually “normal tidal volume”.⁸ We set the tidal volume at 5–6 mL/kg, and conducted pre-experiments referring to relevant literatures.¹³ As long as the double-lumen catheters are well-placed, airway pressure and resistance could be significantly reduced, pulmonary compliance would be improved, and proinflammatory release and inflammatory response would be reduced. PV group showed better results than CV group. This strategy may benefit to patients who suffer from compromised pulmonary function.

The time required for OLV in the operation for esophageal carcinoma is lengthy. All patients received more than two-hour OLV in our study. No sustained hypoxemia or hypercapnia was developed, which suggests that V_T of OLV at 5–6 mL/kg is safe and does not induce insufficiency of oxygen supply and retention of carbon dioxide. This may be attributed to the application of a low PEEP.¹⁴ Considering the effect of inhaled anesthetics on proinflammatory cytokines release, no inhaled anesthetics was used in our study, which was different from other reported studies.^{3,13}

Low tidal volume can possibly result in atelectasis, premature alveolar closure or other complications, particularly during open-chest surgery and the patient is placed at the side-lying position. Cai et al.¹⁵ reported that when the CT scan was performed during two-lung ventilation, low tidal volume did not increase the incidence rate of atelectasis. PEEP has been reported to be effective in preventing alveolar collapse and atelectasis, maintaining opening of the alveoli at end tidal respiration, and also enabling re-opening of the collapsed alveoli.¹⁴ We implemented PEEP in PV group, and extended inhalation time (I:E = 1:1). Chest X-rays showed no indication of atelectasis in the ventilated lung one day after operation, implying low V_T combined with PEEP can effectively prevent occurrence of atelectasis. Whether the protective ventilation strategy can directly reduce pulmonary complications, improve postoperative pulmonary function and so on need further observations.

In summary, performing thoracotomies on OLV support can significantly increase IL6 and IL8 intraoperatively and postoperatively. By adopting the strategy of pulmonary protective ventilation, airway pressure and resistance is remarkably lowered during OLV, release of IL6 and IL8 is significantly reduced during OLV and after operation, thus pulmonary inflammatory response is alleviated.

Acknowledgements

Guangdong Provincial Medical Science Research Foundation (No. 2003236).

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