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Original Article

Lung protective ventilation strategy reduces the incidence of pulmonary complications after combined thoracoscopic and laparoscopic esophagectomy by inhibiting inflammatory response

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Abstract: Background: A lung protective ventilation strategy (LPVS) is critical in treating acute respiratory distress syndrome (ARDS), the severest pulmonary complication after open esophagectomy. Moreover, it may be also helpful in preventing the development of ARDS. Recently, combined thoracoscopic-laparoscopic esophagectomy (TLE) has been widely applied in treating esophageal cancer, and has a lower incidence of post-operative pulmonary complications compared with open esophagectomy. However, the effect of a LPVS applied in the perioperative period of TLE on preventing post-operative pulmonary complications is still not defined. Objectives: To investigate the effect of a LPVS applied in the perioperative period of TLE on preventing post-operative pulmonary complications. Methods: The patients prepared for receiving TLE were randomly allocated into the test and control group. A LPVS was adopted in the test group and a conventional ventilation strategy in the control group. Four time points were determined to observe respiratory mechanics indexes, arterial blood gas indexes and inflammatory factors, including T_1 (10 min after tracheal intubation), T_2 (60 min after one-lung ventilation), T_3 (end of TLE) and T_4 (24 h after TLE). All patients were followed up per day within 10 days after TLE for the incidence of pulmonary complications. Results: 1) For Ppeak, Pplat and Raw, increasing rates from T_1 to T_2 and T_3 were higher in the control group than in the test group; 2) for PaO_2, decreasing rates from T_1 to T_2 and T_3 were lower in the test group than in the control group. For $PetCO_2$, increasing rates from T_1 to T_2 and T_3 were higher in the test group than in the control group; 3) for IL-6, IL-8, TNF-α and CRP, increasing rates from T_1 to T_2, T_3 and T_4 were lower in the test group than in the control group; and 4) incidence of pulmonary complications was higher in the control group than in the test group. Conclusions: A LPVS could reduce the increasing extent of respiratory mechanics indexes, improve oxygenation, and attenuate inflammatory responses in TLE, which might be helpful in decreasing the incidence of pulmonary complications after esophagectomy.

Keywords: Lung protective ventilation strategy, combined thoracoscopic-laparoscopic esophagectomy, pulmonary complications, inflammatory response

Introduction

Pulmonary complications occur frequently after open esophagectomy with an incidence from 20% to 40%, including acute respiratory distress syndrome (ARDS), pulmonary atelectasis, pulmonary infection, pleural effusions, chylothorax, and pulmonary embolism [1]. Among them, ARDS is severest with the highest mortality [2]. A lung protective ventilation strategy is critical in treating ARDS [3], and may be also helpful in preventing the development of ARDS [4]. A lung protective ventilation strategy (LPVS) consists of low tidal volume (V_T), appropriate positive end-expiratory pressure (PEEP), limiting plateau pressure (*P*plat) and recruitment maneuvers (RM) [5-7]. Recently, combined thoracoscopic-laparoscopic esophagectomy (TLE) has been widely applied in treating esophageal cancer [8, 9], and has a lower incidence of post-operative pulmonary complications compared with open esophagectomy [9]. However, the effect of a lung protective ventilation strategy applied in the perioperative period of TLE on preventing post-operative pulmonary complications is still not well defined. In this paper, the

effect of a lung protective ventilation strategy applied in the perioperative period of TLE on preventing post-operative pulmonary complications was compared to a conventional ventilation strategy, and the aim was to provide basis for the application of a lung protective ventilation strategy during the perioperative period of TLE.

Materials and methods

Patients

A total of 160 patients, who were prepared for receiving TLE, were enrolled in Affiliated Tumor Hospital of Xinjiang Medical University from March 2015 to March 2016. Inclusion criteria included (1) esophageal cancer patients diagnosed definitively through the histopathological examination; (2) untreated esophageal cancer patients; (3) patients with an age from 18 to 79 years; and (4) patients prepared for receiving combined thoracoscopic and laparoscopic esophagectomy. Exclusion criteria included (1) patients with severe disorders of cardio-pulmonary function; (2) patients with severe immunological diseases; (3) patients with severe damage of hepatorenal function; (4) patients undergoing preoperative radiotherapy and chemotherapy; and (5) open esophagectomy adopted alternatively because of misoperation or severe pleural adhesions. Both ASA and NYHA grade were I or II for all patients. A single-lumen endotracheal intubation and continuous CO_2 insufflation were used during general anesthesia.

This study received the permission of the ethic committee of Affiliated Tumor Hospital of Xinjiang Medical University (2015002), and all patients provided informed consent. The trial registration number was ChiCTR-IOR-150098-96.

Grouping

All patients were randomly allocated into a test group and a control group. A lung protective ventilation strategy was adopted in the test group and a conventional ventilation strategy in the control group. A lung protective ventilation strategy consisted of low tidal volume (V_T) (6 ml/Kg), low positive end-expiratory pressure (PEEP) (5 cmH_2O, 1 cmH_2O = 0.098 kPa), Pplat ≤ 30 cmH_2O and recruitment maneuvers (RM) [5-8]. A conventional ventilation strategy only consisted of V_T (9 ml/Kg).

Anesthesia

Preoperative preparation consisted of respiratory tract preparation, nutrition support and exercise of respiratory function. Exercise of respiratory function included deep-breathing exercise and climbing stairs. Fasting for 8 hours and water-deprivation for 4 hours were adopted preoperatively. Blood pressure (BP), heart rate (HR), respiration, electrocardiogram (ECG) and oxygen saturation (SpO_2) were routinely monitored for all patients after they entered the operating room. A 14F double cavity central venous catheter was placed under the right clavicle with a depth of 12-13 cm under local anesthesia for monitoring the central venous pressure (CVP) and maintaining the infusion approach. A disposable venous indwelling needle (Introcan Safety®-W, 22G*1", 35 ml/min) was placed through puncturing the radial artery under local anesthesia for monitoring the invasive blood pressure (IBP). The BP and HR kept for 5 min were defined as the basal level. A single-lumen endotracheal tube (SLET) with an inner diameter of 7.5 mm or 8.0 mm was introduced to a depth of 22-24 cm. Anesthesia was maintained through keeping 1% of sevoflurane at the end expiratory, 0.08-0.15/ug·min^{-1}·kg^{-1} of sufentanil, 3-4 mg·kg^{-1}·h^{-1} of propofol and 0.06-0.08 mg·kg^{-1}·h^{-1} of cis-atracurium. An EEG Monitor with BIS (Aspect Medical Systems Inc., USA) was used in monitoring the depth of sedation, and the value of BIS was maintained for 40-60. When the fluctuation of BP and HR was less than 20% of the basal level, patients adopted the left lateral decubitus position and inclined forward (about 15°). A thoracoscope entered the chest from the right side, and the upper limb of the affected side raised forward and was stabilized at a hand bracket. After the thoracoscope entered the chest, ventilation was paused, and the right chest received persistent CO_2 at 2 L/min. The pressure in the chest was kept at 8-10 mmHg for forming the artificial pneumothorax which compressed the right lung and made it collapse. Mechanical ventilation was performed with Drager Fabius 2000 Anesthesia system (Drager, Germany), and the parameters at two-lung ventilation (TLV) and one-lung ventilation (OLV) were as follows: a pressure control model was adopted

Table 1. General data of the test and control group

	Test group (n = 79)	Control group (n = 78)	χ^2/t	*P*
Male/Female	55/24	48/30	1.136	0.286
Age	63.29±6.34	62.18±7.74	0.698	0.516
BMI	22.95±4.92	24.18±5.47	0.878	0.382
Tumor position				
Upper thoracic portion	10	23		
Mid-thoracic portion	50	42	1.466	0.481
Lower thoracic portion	11	13		
Pathological types				
Squamous cell carcinoma	45	51	1.172	0.279
Non-squamous cell carcinoma	34	27		
TNM staging				
I	13	18		
II	35	36	1.705	0.426
III	31	24		
FEV1/FVC	83.64±13.2	86.13±8.3	1.025	0.257
Medical history of respiratory diseases				
COPD	11	8		
Asthma	2	3	0.675	0.714
None	66	67		
Operation time (min)	312.25±62.8	323.76±56.3	0.857	0.391
Blood loss during operation (ml)	250.62±62.4	265.68±47.2	1.218	0.187

BMI: Body mass index; FEV1/FVC: Forced vital capacity rate of one second; COPD: Chronic obstructive pulmonary disease.

during the operation. The test group employed a lung protective ventilation strategy consisting of V_T (6 ml/Kg), PEEP (5 cmH_2O) and Pplat ≤ 30 cmH_2O with a ventilation frequency of 20 times/min and inspiration and expiration ratio (I/E) of 1:2; the control group employed a conventional ventilation strategy of V_T (9 ml/Kg) with a ventilation frequency of 12 times/min and I/E of 1:2. Both the test and control group adopted a fraction of inspiration O_2 (FiO_2) of 100%. Respiratory parameters should be timely regulated according to $PetCO_2$ and Paw in order to attenuate barotrauma in both the test group and control group. Inflation manually controlled was performed in both the test group and control group with a simply respirator before closing chest for five times, and TLV was then recovered after clearing the airway. Following, the test group employed a RM method consisting of PC 40 cmH_2O, PEEP 0 cmH_2O and FiO_2 100% for 40 s, and the control group employed a conventional inflation manually controlled for 5-10 times. The criteria for extubation after operation included (1) patients were conscious; (2) patients had stable vital signs; (3) reflection of tussis recovered; (4) patients had good muscle tone; and (5) the results of spontaneous breathing test (SBT) [10] supported extubation.

Observed indexes

Four time points were determined to observe respiratory mechanics indexes, arterial blood gas (ABG) indexes and inflammatory factors according to the reference, including T_1 (10 min after racheal intubation), T_2 (60 min after one-lung ventilation), T_3 (end of TLE) and T_4 (24 h after TLE) [11]. Respiratory mechanics indexes included Ppeak, Pplat and Raw at T_1, T_2 and T_3. ABG samples were collected at T_1, T_2, T_3 and T_4 for measuring PaO_2, $PaCO_2$, $PetCO_2$ and PH. Venous blood samples of 2 ml were also collected at T_1, T_2, T_3 and T_4 for measuring interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α) with enzyme-linked immunoabsorbent assay (ELISA) and C-reactive protein (CRP) with rate nephelometry.

All patients were followed up per day within 10 days after TLE. Pulmonary infection, pulmonary atelectasis, pulmonary edema, bronchial spasm, hypoxemia, pneumothorax and ARDS were recorded.

Statistical analysis

All data were analyzed with the SPSS version 19.0 for Windows (SPSS Inc., USA). Quantitative variables were expressed as mean ± SD and qualitative variables as percentage. Quantitative variables were analyzed with Student's t test, and qualitative variables with chi-square test or Fisher exact test. Significance was set at $P<0.05$.

Table 2. Respiratory mechanics indexes at T_1, T_2 and T_3 in the test and control group

	Ppeak (mmHg)	Pplat (mmHg)	Raw ($cmH_2O \cdot L^{-1} \cdot S^{-1}$)
Test group			
T_1	18.46±2.84	15.26±2.57	13.56±1.77
T_2	26.54±3.61*	20.29±3.15*	20.32±3.35*
T_3	22.53±3.27*	17.48±2.64*	18.54±2.59*
Control group			
T_1	17.18±3.66	15.34±2.61	13.61±2.75
T_2	33.57±2.89*	28.23±4.37*	26.31±3.68*
T_3	31.46±4.71*	22.46±4.15*	21.73±3.29*

*: $P<0.05$, vs T_1.

Table 3. An increasing rate (IR) of respiratory mechanics indexes at T_2 and T_3 ($IR_n = (T_n-T_1)/T_1*100\%$, n = 2, 3) in the test and control group

	Ppeak (%)	Pplat (%)	Raw (%)
Test group			
IR_2	43.24±13.68	32.96±14.03	49.85±13.92
IR_3	38.52±12.57	14.55±6.38	36.72±9.79
Control group			
IR_2	94.78±32.64*	84.03±28.74*	93.31±29.05*
IR_3	92.86±29.85#	46.41±12.87#	59.66±13.58#

*: $P<0.05$, vs IR_2 of test group; #: $P<0.05$, vs IR_3 of test group.

Table 4. ABG indexes at T_1, T_2, T_3 and T_4 in the test and control group

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	$PetCO_2$ (mmHg)	PH
Test group				
T_1	344.56±38.67	39.94±4.27	32.85±3.79	7.42±0.12
T_2	259.83±41.29*	43.02±5.12	38.04±3.88*	7.35±0.09
T_3	228.27±34.56*	42.34±4.25	35.63±3.58*	7.36±0.15
T_4	339.37±35.67	40.37±3.81	32.96±3.35	7.41±0.14
Control group				
T_1	343.72±36.58	39.32±4.94	32.78±3.89	7.41±0.11
T_2	187.45±29.21*	44.86±5.93	42.17±4.15*	7.36±0.13
T_3	164.65±31.67*	42.58±4.62	39.39±3.57*	7.35±0.15
T_4	336.54±32.68	40.87±3.86	33.06±3.44	7.42±0.10

Arterial blood gas: ABG; *: $P<0.05$, vs T_1.

Results

General data

One patient was excluded from this study because open esophagectomy was adopted alternatively because of severe pleural adhesions in the test group, and two patients were excluded because of misoperation. The test group was not statistically different from the control group in male/female, age, body mass index (BMI), tumor position, pathological types, TNM staging, forced vital capacity rate of one second (FEV1/FVC), medical history of respiratory diseases, operation time and blood loss during operation (all $P>0.05$, Shown in **Table 1**).

Comparison of respiratory mechanics indexes

For both the test and control group, Ppeak, Pplat and Raw were higher at T_2 and T_3 than at T_1 (all $P<0.05$, Shown in **Table 2**). For Ppeak, Pplat and Raw, the increasing rates from T_1 to T_2 and T_3 were higher in the control group than in the test group (all $P<0.05$, Shown in **Table 3**).

Comparison of ABG indexes

For both the test and control group, PaO_2 was lower at T_2 and T_3 than at T_1 (all $P<0.05$) and not statistically different between T4 and T_1 (all $P>0.05$), $PetCO_2$ was higher at T_2 and T_3 than at T_1 (all $P<0.05$) and not statistically different between T_4 and T_1 (all $P>0.05$), and both $PaCO_2$ and PH were not statistically different between these time points (all $P>0.05$, Shown in **Table 4**). For PaO_2, the decreasing rates from T_1 to T_2 and T_3 were lower in the test group than in the control group (all $P<0.05$). For $PetCO_2$, the increasing rates from T_1 to T_2 and T_3 were higher in the test group than in the control group (all $P<0.05$, Shown in **Table 5**).

Comparison of inflammatory factors

IL-6, IL-8, TNF-α and CRP were higher at T_2, T_3 and T4 than at T_1 in both the test and control group (all $P<0.05$, Shown in **Table 6**). The increasing rates from T_1 to T_2, T_3 and T_4 were

Table 5. Decreasing rate (DR) of PaO_2 and increasing rate (IR) of $PetCO_2$ at T_2 and T_3 ($IR_n/DR_n = (T_n-T_1)/T_1*100\%$, n = 2, 3) in the test and control group

	DR of PaO_2	IR of $PetCO_2$
Test group		
DR_2/IR_2	-3.56±1.74	15.80±5.63
DR_3/IR_3	0.40±0.18	8.48±2.56
Control group		
DR_2/IR_2	-21.61±11.36*	28.65±10.18*
DR_3/IR_3	-16.44±7.29#	20.16±4.93#

*: $P<0.05$, vs DR_2/IR_2 of test group; #: $P<0.05$, vs DR_3/IR_3 of test group.

Table 6. Inflammatory factors at T_1, T_2, T_3 and T_4 in the test and control group

	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF-α (pg/ml)	CRP (mg/L)
Test group				
T_1	155.62±35.2	15.54±3.2	157.58±34.7	7.51±3.52
T_2	193.24±27.4*	19.33±2.5*	257.73±65.8*	20.33±6.7*
T_3	232.31±41.1*	23.24±4.6*	364.24±46.3*	34.24±7.1*
T_4	213.25±48.3*	21.26±4.3*	293.22±45.8*	45.75±5.8*
Control group				
T_1	161.63±32.5	15.51±3.5	155.62±35.2	8.62±3.2
T_2	252.46±26.7*	24.38±2.7*	362.36±27.6*	29.29±2.7*
T_3	347.37±48.6*	36.29±4.1*	436.38±41.6*	45.36±4.6*
T_4	326.28±45.3*	34.27±4.8*	393.29±48.3*	78.27±4.3*

*: $P<0.05$, vs T_1.

lower in the test group than in the control group for IL-6, IL-8, TNF-α and CRP (all $P<0.05$, Shown in **Table 7**).

Comparison of pulmonary complications

The total incidence of pulmonary complications was 17.72% (14/79) in the test group, including 7 cases of pulmonary infection, 6 cases of pulmonary atelectasis, 5 cases of pulmonary edema, 6 cases of bronchial spasm and 10 cases of hypoxemia. The total incidence of pulmonary complications was 32.05% (25/78) in the control group, including 16 cases of pulmonary infection, 16 cases of pulmonary atelectasis, 13 cases of pulmonary edema, 14 cases of bronchial spasm, 20 cases of hypoxemia and 2 cases of ARDS. The incidence of total pulmonary complications was higher in the control group than in the test group ($\chi^2 = 4.317$, $P<0.05$).

Discussion

A LPVS is based on low V_T (4-6 ml/kg) and meanwhile employs RM and PEEP, which is firstly applied in treating ARDS. A LPVS can reduce the airway pressure and shear force resulting from alveolar overinflation, and decrease the loss of alveolar surfactant and release of inflammatory factors resulting from the mechanical stimulation on pulmonary epithelial cells, which can effectively reduce the incidence and mortality of ARDS through attenuating the injury of pulmonary tissue and inflammatory response in the lung and even in the whole body [12]. Recently, a LPVS begins to be applied in treating non-ARDS patients. Sutherasan Y et al [13] indicate that a LPVS can reduce the incidence of ARDS, pulmonary atelectasis and pulmonary infection. Serpa Neto et al [14] and Gu et al [15] indicate that low V_T can attenuate the pulmonary injury during perioperative period and reduce the risk of pulmonary infection after operation.

Pplat ≤ 30 cmH_2O can improve the statistic and dynamic compliance of the lung, maintain oxygenation and increase the ventilation of dead space by attenuating barotrauma; PEEP can prevent alveolar collapse and pulmonary atelectasis effectively and keep the relative opening of alveoli at end-expiratory, and meanwhile can also make the collapsed alveoli re-open; compared with conventional high V_T, combined low V_T and appropriate PEEP can improve alveolar recruitment, pulmonary function and oxygenation [16]. However, excessive PEEP may increase the incidence of the fluctuation of inspiratory plateau pressure and hemodynamics. An animal experiment [17] shows that the inflammatory cells in the pulmonary tissue were significantly less in the group receiving combined V_T = 5 ml/kg and PEEP = 5 cmH_2O than in the other two groups receiving either combined V_T = 5 ml/kg and PEEP = 2 cmH_2O or combined V_T = 10 ml/kg and PEEP = 2 cmH_2O. Nowadays, 5 cmH_2O is thought as the best value for PEEP, which may improve the state of hypoxemia through promoting oxygenation and reduce the incidence of the pulmonary injury

Table 7. Increasing rate (IR) of inflammatory factors at T_2, T_3 and T_4 (IR_n = $(T_n-T_1)/T_1*100\%$, n = 2, 3, 4) in the test and control group

	IL-6	IL-8	TNF-α	CRP
Test group				
IR_2	24.16±11.49	24.39±10.84	63.56±28.27	170.70±46.83
IR_3	49.29±30.18	49.55±31.47	131.15±31.45	354.92±48.75
IR_4	37.02±18.37	36.81±20.36	86.08±36.74	508.19±69.48
Control group				
IR_2	56.19±23.72*	57.19±21.35*	132.85±40.38*	237.79±53.49*
IR_3	114.91±52.64#	133.98±53.47#	180.41±42.85#	425.62±52.82#
IR_4	101.86±44.68☆	120.95±47.68☆	152.72±41.73☆	806.07±97.38☆

*: $P<0.05$, vs IR_2 of test group; #: $P<0.05$, vs IR_3 of test group; ☆: $P<0.05$, vs IR_4 of test group.

[18]. In another study [19], the value of PEEP is observed and recorded at the biggest dynamic compliance of the lung through PEEP titration, which is defined as the best PEEP value. However, this method is difficult to manipulate in clinical practice, and the evidence is not enough. Therefore, the optimal PEEP value remains controversial. Wang W et al [20] performs a RM consisting of 10 continuous artificial ventilation before a one-lung ventilation and make Pplat up to 40 cmH_2O, and mechanical ventilation is then employed with PEEP of 15-20 cmH_2O until a one-lung ventilation is performed, which can not only decrease dead space, but also improve the oxygenation during one-lung ventilation.

The conventional ventilation method was high V_T of 10-12 ml/kg in the anesthesia of esophageal cancer operations, which is one of high-risk factors for the acute lung injury after operation. In this study, both the test and control group employed a pressure controlled model. The test group employed a LPVS consisting of low V_T (6 ml/Kg), low PEEP (5 cmH_2O), Pplat ≤ 30 cmH_2O and RM, and the control group employed a conventional ventilation strategy consisting of V_T (9 ml/Kg). Our results showed that respiratory mechanics indexes (Ppeak, Pplat and Raw) were higher in T_2 and T_3 than in T_1 in both the test and control group, but the increasing rates of these respiratory mechanics indexes from T_1 to T_2 and T_3 decreased significantly in the test group compared with in the control group; PaO_2 was lower in T_2 and T_3 than in T_1 in both the test and control group, but the decreasing rates of PaO_2 from T_1 to T_2 and T_3 decreased significantly in the test group compared to in the control group, which suggested a better oxygenation in the test group.

Continuous CO_2 insufflation can cause hypercapnia, and prolonged hypercapnia can increase the risk of pulmonary hypertension, disorders of the intracranial pressure and dysrthymias [6]. In our study, respiratory rate was adjusted according to the dynamic monitoring results of $PetCO_2$ and ABG in order to guarantee an effective minute volume, regulate I/E and promote the excretion of CO_2. Therefore, $PaCO_2$ did not increase significantly in both the test and control group. Moreover, a RM was also used in the test group at the end of one-lung ventilation after operation. This strategy can guarantee the full recruitment of alveoli and prevent the development of pulmonary infection and pulmonary atelectasis. Our results showed that the inflammatory indexes (IL-6, IL-8, TNF-α and CRP) increased significantly at T_2, T_3 and T_4 compared at T_1 in both the test and control group, which indicated that the stress response resulting from esophagectomy caused the release of inflammatory factors. However, the increasing rates of these inflammatory factors from T_1 to T_2, T_3 and T_4 decreased significantly in the test group compared to in the control group. This result suggested that a LPVS could attenuate the stimulus resulting from ventilation on alveoli, and decrease the release of inflammatory factors and attenuate the stress response of operation in TLE. In our study, the incidence of total pulmonary complications was higher in the control group than in the test group, which might be able to be explained by the fact that a LPVS could reduce the increasing extent of respiratory mechanics indexes, improve oxygenation, and attenuate inflammatory responses in TLE.

In conclusion, a LPVS could reduce the increasing extent of respiratory mechanics indexes, improve oxygenation, and attenuate inflammatory responses in TLE, which might play a role in reducing the incidence of pulmonary complications after esophagectomy.

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Disclosure of conflict of interest

None.

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