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Original Article

The effects of pressure-controlled ventilation on the pulmonary function and inflammatory responses of elderly patients undergoing esophageal cancer radical operations

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Abstract: Objective: To determine the effects of different one-lung ventilation modes on the pulmonary function and serum inflammatory responses of elderly patients undergoing esophageal cancer radical operations during the perioperative period. Methods: A total of 118 patients undergoing esophageal cancer operations were enrolled and randomly assigned to a control group and an observation group (n=59 each). The patients in the observation group were treated with pressure-controlled ventilation, and the patients in the control group were treated with conventional volume-controlled ventilation. The following indexes of the two groups were analyzed and compared: the average peak airway pressure (Ppeak) before the operations (T0), after 30 min of one-lung ventilation (T1), after 60 min of one-lung ventilation (T2), and after another 30 min of two-lung ventilation (T3), the oxygenation indexes and the inflammatory factors (interleukin-6 (IL-6) and interleukin-8 (IL-8)) before and after the operations, and the postoperative pulmonary infection scores. Results: At T1, T2, and T3, the average Ppeak of the observation group was lower than it was in the control group (P<0.05). In addition, after the operations, the observation group showed higher oxygenation indexes and lower IL-6 and IL-8 levels in the peripheral blood than the control group and also had a lower pulmonary infection score than the control group (all P<0.05). Conclusion: Pressure-controlled ventilation can effectively lower the airway pressure, the inflammatory factor levels, and the lung infection scores for elderly patients undergoing esophageal cancer operations, so it can protect the pulmonary function of the patients in clinical practice to a certain extent.

Keywords: Esophageal cancer radical operation, pressure-controlled ventilation, pulmonary injury, inflammatory response, function protection

Introduction

Esophageal cancer is one of the most common malignant tumors in the digestive tract. Current studies have confirmed that a variety of factors are related to the development of esophageal cancer, mainly including advanced age, heredity, obesity, the living environment, eating habits, and poor lifestyle choices (smoking and a preference for hot food) [1, 2]. According to published studies, the incidence of esophageal cancer in China is 21.7/100,000, accounting for about 8% of the incidence of all malignant tumors, and with the aggravation of aging in China, the incidence is increasing annually [3-5].

At present, an esophageal cancer radical operation is the main treatment for esophageal cancer, and one-lung ventilation-based anesthesia is mainly adopted during it, a technique that contributes to protecting the contralateral pulmonary function and provides a clear surgical field of vision for the operation [6-9]. However, patients with esophageal cancer are mainly middle-aged and elderly people who suffer from poor diets caused by esophageal tumors, so most patients with esophageal cancer suffer from metabolic disorders and malnutrition in different degrees before their operations, which will eventually lower their tolerance to anesthesia and surgery. In addition, pulmonary shunt

and the imbalance of the ventilation ratio caused by one-lung ventilation aggravates patients' postoperative pulmonary function injuries [10, 11].

Volume-controlled ventilation and pressure-controlled ventilation are the main modes of one-lung ventilation, and volume-controlled ventilation is most commonly used in clinical practice [12]. However, some studies have revealed that volume-controlled ventilation activates inflammatory cells, induces the release of inflammatory mediators, giving rise to pulmonary injuries. In addition, some researchers have preliminarily confirmed that pressure-controlled ventilation can effectively improve the pulmonary function of patients with respiratory failure [13], but there is still little research on one-lung ventilation for patients with esophageal cancer. Therefore, this study explored the effects of pressure-controlled ventilation on the pulmonary function and inflammatory response of elderly patients undergoing esophageal cancer radical operations.

Materials and methods

General data

A total of 118 patients undergoing esophageal cancer operations at The Affiliated Yantai Yuhuangding Hospital of Qingdao Univeristy from January 2018 to December 2019 were enrolled and randomly assigned to a control group and an observation group (n=59 each). The inclusion criteria were as follows: Patients diagnosed with esophageal cancer through a gastroscopy biopsy, patients 60 years old or older, patients without contraindications for general anesthesia operations, patients at grades II-III in the American Society of Anesthesiologists (ASA) grading system before their operations, and those without contraindications for one-lung ventilation (i.e., those with serious lung diseases or thoracic deformities). The exclusion criteria were as follows: Patients with a history of lung surgery, patients who had undergone thoracic surgery, patients with other comorbid organ dysfunctions, patients infected before the operation, and those who had taken glucocorticoids against immune system diseases. All the enrolled patients signed informed consent forms after learning about the study, and the study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao Univeristy.

Methods

Anesthesia methods and operation methods: Each patient was intramuscularly injected with 0.1 g phenobarbital (New Asia Pharmaceutical Co., Ltd., Shanghai, China) to relieve tension and 0.5 mg atropine (Yuancheng Technology Development Co., Ltd., Wuhan, China) to reduce airway secretion half an hour before the operation. In the research center, the anesthesia induction was carried out on each patient with 0.05 mg/kg midazolam (Nhwa Pharmaceutical Co., Ltd., Jiangsu, China), 0.5-0.6 μg/kg sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Hubei, China), 0.15 mg/kg cisatracurium (Hengrui Medicine Co., Ltd., Jiangsu China), and 1.0-2.0 mg/kg propofol (Southwest Pharmaceutical Co., Ltd., Chongqing, China), and the anesthesia was maintained using the inhalation of 2% sevoflurane (Xiyuan Biotechnology Co., Ltd., Shanghai, China) and intravenous injections of 5 mg/h cisatracurium and 0.1-0.3 μg/(kg.min) remifentanil (China National Pharmaceutical Industry Cooperation Ltd., China) with a syringe pump. Each patient in the group received anastomosis at the right upper thoracic part through the two incisions in the right chest and the middle of the upper abdomen under general anesthesia through a thoracotomy for the resection of esophageal cancer.

Ventilation methods: All the patients were given volume-controlled ventilation after intubation: tidal volume: 8 mL/kg; frequency: 12 times/min; respiratory ratio: 2:1; inhaled concentration of oxygen: 100%; oxygen flow: 1 L/min. According to the admission conditions, the patients in the two groups were given different ventilation control modes during the left-lung ventilation with respiratory parameters adjusted as follows: Respiratory frequency: 12-16 times/min. $P_{ET}CO_2$ was ensured to be within 35-45 mmHg (end tidal carbon dioxide partial pressure, combined with blood gas analysis if necessary) by adjusting the respiratory frequency. The patients in the control group were given volume-controlled one-lung ventilation at a tidal volume of 6 mL/kg, and the patients in the observation group were given pressure-controlled one-lung ventilation using one-lung ventilation first, followed by pressure-controlled

ventilation at the inhalation peak pressure setting after the airway pressure was adjusted to 6 mL/kg. The inhaled concentration of oxygen was 100%, and the oxygen flow was 1 L/min. The peripheral oxygen saturation was maintained above 90% during the operation. If it was lower than 90%, the oxygen was inhaled through a sputum suction tube on the collapsed side (oxygen saturation can be maintained above 90% by this method in the center). During the operation, both groups of patients were not given positive end-expiratory pressure (PEEP) ventilation during one-lung ventilation, and sputum suction was routinely performed during the transformation from one-lung ventilation to two-lung ventilation. After the operation, the patients were given single lumen endotracheal intubation and returned to the ICU. When the patients were fully awake, their muscle strength was evaluated, and their tracheal intubation was pulled out after they passed the spontaneous breathing trial.

Outcome measures

Related indexes of pulmonary function: We measured the peak airway pressure (Ppeak) before the operation (T0), after 30 min of one-lung ventilation (T1), after 60 min of one-lung ventilation (T2), and after another 30 min of two-lung ventilation (T3), and the oxygenation indexes including the arterial oxygen partial pressure (PaO_2) and the inspired oxygen fraction (FiO_2) before and after operation.

Inflammatory factors IL-6 and IL-8: Peripheral venous blood (6-8 mL) was sampled from each patient in the two groups before the operation and at 24 h after the operation , placed in anticoagulant tubes, and centrifuged at 3,000 r/min in a centrifuge to take the supernatant, and then the supernatant was stored at -80°C for later analysis. The serum interleukin-6 (IL-6) and interleukin-8 (IL-8) levels in the sampled blood were determined using an enzyme-linked immunosorbent assay (ELISA) Kit (enzyme immunoassay analyzer: Infinite F50, Tecan, Switzerland; Kit: Santa, USA) in accordance with the kit's instructions.

Comparison of the pulmonary infection scores: The pulmonary infections of each patient were scored at 48 after the operation and were mainly based on six measurements from each patient: Body temperature, white blood cell count in hemogram, airway secretions, oxygenation index, infiltration shadow on the chest x-ray film, and airway aspirate culture. Each item was assigned 0-2 points, and the maximum total score was 12 points. A higher score indicated a more severe condition [14].

Statistics

All the data were analyzed using SPSS 22.0. The measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± SD), and the comparisons between groups were done using independent sample T tests. The repeated measurement data were analyzed using the repeated measures analysis of variance, and the intra-group pairwise comparisons were carried out using LSD-t tests. The enumeration data were expressed as the number of cases/percentage (n/%) and were compared between groups using chi-squared tests. α=0.05 was taken as the test standard, and P<0.05 indicated a significant difference.

Results

Comparison of the baseline data

The results of this study revealed that there were no significant differences between the two groups in terms of sex, age, hypertension, diabetes mellitus, body mass index, or tumor site (all P>0.05), so the two groups were comparable. See **Table 1**.

Comparison of the data gathered during surgery in the two groups

The results of this study revealed that there was no significant differences between the two groups in their operation times, anesthesia times, one-lung ventilation times during the operation, or intraoperative blood loss (all P>0.05). See **Table 2**.

Comparison of average Ppeak between the two groups at each time point

The results of this study revealed that at T0, there was no significant difference between the two groups in their average Ppeak, but at T1, T2, and T3, the average Ppeak of the observation group was lower than it was in the control group (all P<0.05). See **Table 3**.

Table 1. Comparison of baseline data (($\bar{x}$ ± sd), n/%)

Group	Control group	Observation group	t/χ^2	P
Sex (male/female)	44/15	42/17	0.0429	0.836
Age (year)	72.5±3.1	71.9±2.8	1.103	0.272
Hypertension (n)	11	9	0.060	0.806
History of smoking (n)	19	16	0.366	0.545
History of drinking (n)	23	18	0.934	0.334
Diabetes mellitus (n)	7	9	0.072	0.788
Malnutrition (n)	4	6	0.437	0.509
BMI (kg/m^2)	23.81±0.78	23.24±0.81	1.366	0.175
Stage of esophageal cancer (I/II, n)	32/27	28/31	0.543	0.461
Stage of ASA (II/III, n)	30/29	32/27	0.206	0.65
Tumor site (n)				
Epimere	10	11	0.696	0.706
Mesomere	40	42		
Hypomere	9	6		

Note: BMI: body mass index.

Table 2. Comparison of the data during surgery

Group	Control group	Observation group	t	P
Operation time	165.4±23.2	169.3±24.1	0.896	0.372
One-lung ventilation time	129.8±27.4	132.9±24.9	0.643	0.521
Intraoperative blood loss	319.1±82.8	324.2±84.5	0.331	0.741
Anesthesia time	189.8±29.4	194.3±30.1	0.821	0.413

Table 3. Comparison of the average peak airway pressure at each detection point

Group	Control group	Observation group	t	P
Average peak airway pressure (cmH_2O)				
T0	14.9±5.2	15.1±5.1	0.211	0.833
T1	24.4±3.8	23.1±3.3	2.172	0.032
T2	25.8±4.1	23.7±3.9	2.851	0.005
T3	21.1±3.7	17.4±4.2	5.007	0.000
F group		8.681		0.000
F time		14.319		0.000
F interaction		4.648		0.376

Note: T0: average peak airway pressure before the operation; T1: average peak airway pressure after 30 min of one-lung ventilation; T2: average peak airway pressure after 60 min of one-lung ventilation; T3: average peak airway pressure after another 30 min of two-lung ventilation.

Comparison of the inflammatory factors (IL-6 and IL-8) in the peripheral blood

The results of this study revealed that before the operations, there were no significant differences between the two groups in their IL-6 and IL-8 levels, but after the treatment, both groups showed increased levels of IL-6 and IL-8 (both $P<0.05$), and the IL-6 and IL-8 levels in the observation group were both lower than those in the control group (both $P<0.05$). See **Figures 1** and **2**.

Comparison of the oxygenation indexes before and after the operation and the pulmonary infection scores after the operations

The results of this study revealed that before the operations, there was no difference in the oxygenation indexes in the two groups, but after the operations, the oxygenation indexes of the observation group were significantly higher than the indexes in the control group ($P<0.05$). In addition, after the operations, the pulmonary infection score in the observation group was lower than the pulmonary infection score in the control group ($P<0.001$). See **Table 4**.

Discussion

Esophageal cancer radical operation is the main clinical treatment method for esophageal cancer at present, and one-lung ventilation used during it can not only provide a clearer surgical field of vision, but it can also effectively isolate the two lungs to avoid cross infection, so it can be adopted as a ventilation method during the operation [15,

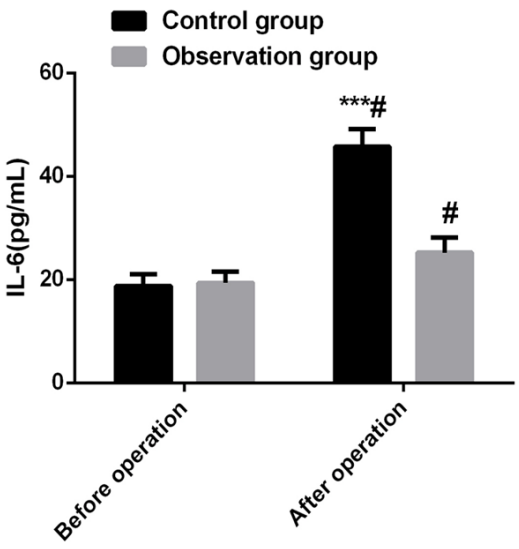

Figure 1. Comparison of IL-6 in the peripheral blood. IL: inflammatory. Compared with before the operation, #P<0.05; compared with after the operation in the observation group, ***P<0.001.

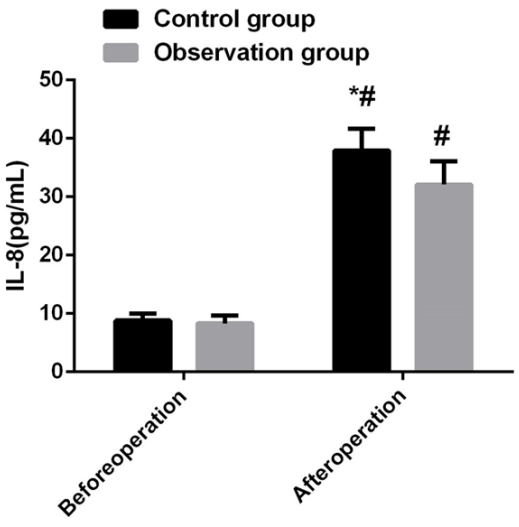

Figure 2. Comparison of the IL-8 in the peripheral blood. IL: inflammatory. Compared with before the operation, #P<0.05; compared with after the operation in the observation group, *P<0.05.

16]. However, recent studies have shown that the improper use of one-lung ventilation technology will damage the lung tissues, and its main related factors include tidal volume and Ppeak [17]. Therefore, the current single lung protection measures serve mainly to reduce tidal volume and airway pressure, which are mainly achieved by regulating and controlling the alveolar pressure and transmural pressure by controlling pressure and volume to avoid excessive expansion and collapse of the alveoli and reduce shear force.

The current one-lung ventilation mode mainly includes pressure-controlled ventilation and volume-controlled ventilation modes. Volume-controlled ventilation usually enhances airway pressure and intrapulmonary shunt and reduces lung oxygenation capacity, and pressure-controlled ventilation makes up for the deficiency of volume-controlled ventilation, which can reduce airway pressure, thus alleviating the clinical lung tissue injury. In this study, the Ppeak of the patients in the observation group was lower than it was in the control group, which preliminarily indicated that the pressure-controlled ventilation can effectively lower the airway pressure, thus providing a protective effect on the pulmonary function. Similar conclusions have been obtained in some previous studies [18].

Studies have confirmed that intraoperative traction, the expansion of the lung tissue itself, and the trauma caused by the operation give rise to the release of the inflammatory factors, mainly including IL-6 and IL-8. IL-6 is the strongest inflammatory factor of stress and loss in thoracic surgery for esophageal cancer, and IL-8 is the specific cytokine of lung tissue injury, which is produced by macrophages and has a strong leukocyte chemotaxis. Moreover, in this study, the levels of the serum inflammatory factors (IL-6 and IL-8) in the control group were higher than those in the observation group, which may be related to the fact that the injuries caused by the volume-controlled ventilation and the injury of the airway caused by pressure gave rise to an inflammatory cascade, induced an inflammatory reaction, and finally resulted in the elevation of the inflammatory factors in the body, events that support the earlier research results [19, 20].

The postoperative oxygenation indexes and the pulmonary infection score are the main evaluation indexes for pulmonary injuries under different ventilation modes. In this study, the oxygenation indexes of the observation group were higher than the indexes in the control group, and the pulmonary infection score of the observation group was lower than the score in the control group, which implies that pressure-con-

Table 4. Comparison of the oxygenation indexes before and after the operations and the pulmonary infection scores after the operation

Group	Control group	Observation group	t	P
Oxygenation indexes				
Before the operations	440.3±78.2	451.1±72.9	0.776	0.439
After the operations	400.8±67.3	428.7±65.1	2.289	0.024
Pulmonary infection score	4.9±1.3	3.8±1.7	3.948	0.000

trolled ventilation can reduce intrapulmonary shunt and dead space ventilation, improve the pulmonary blood flow distribution and pulmonary blood flow ratio, and alleviate the inflammatory reaction in lung tissues, thus effectively protecting the pulmonary function of patients with esophageal cancer. Similar studies have been reported before [21]. However, the cohort in this study was small and the study is a single-center study, so it was not necessary to carry out a multi-center prospective randomized controlled study with a large-sample size to confirm the conclusions of this study. In addition, a more effective evaluation index is also the main guarantee for improving the benefits of pressure-controlled ventilation on pulmonary function.

To sum up, this study has confirmed that pressure-controlled ventilation can effectively lower the intraoperative airway pressure of patients with esophageal cancer during one-lung ventilation and can alleviate the inflammatory response, improve the oxygenation indexes, and lower patients' pulmonary infection scores, so it is conducive to the recovery of patients' pulmonary functions after an operation.

Disclosure of conflict of interest

None.

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