Correlation between controlled lung collapse and early lung injury in dogs

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Received September 29, 2017; Accepted June 27, 2018

DOI: 10.3892/etm.2018.6531

Abstract. A new type of pulmonary sequestration ventilator was used to compare the relationship between controlled lung collapse and early lung injury in thoracic surgery for dogs. Eighteen experimental dogs were randomly divided into three groups (G1-G3 groups). After general anesthesia, the shunt balance in lung was controlled and the pulmonary sequestration tube was placed in the femoral artery and vein, and the Swan-Ganz tube was placed into the right internal jugular vein as well. Two-lung ventilation (TLV) was first performed for 20 min, followed by one-lung ventilation (OLV). The degree of collapse was 100% (G1), 90% (G2), and 50% (G3). Blood samples were extracted from femoral artery and jugular vein prior to collapse (T0), and at 30 (T1), 60 (T2), and 120 (T3) min after collapse for blood gas analysis to determine the shunt ratio (Qs/Qt). Blood samples were also subjected to enzyme linked immunosorbent assay (ELISA) to determine serum tumor necrosis factor- α (TNF- α), intercellular immune adhesion molecule-1 (ICAM-1) and interleukin-6 (IL-6) levels. Arterial blood pressure, heart rate, pulmonary artery pressure and other physiological indicators were monitored during the experiment. Lung tissues were collected at T3 to calculate the wet/dry weight ratio (W/D). Histopathological changes were observed and compared by microscopic observation and blind scoring of pathological section after hematoxylin and

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Key words: one lung ventilation, lung collapse degree, lung injury

eosin (H&E) staining. There were no significant differences in the physiological indexes between the two groups during TLV (P>0.05). Mean pulmonary arterial pressure (MPAP) in G2 and G3 groups was significantly more stable than that in G1 group after OLV (P<0.05); shunt ratio Qs/Qt, W/D, and serum TNF- α , ICAM-1 and IL-6 levels in the lung were decreased; and the degrees of pulmonary edema, hemorrhage, inflammatory cell infiltration and lung injury were also decreased. There was no statistically significant difference in each index at each time-point between G2 and G3 groups (P>0.05). Compared with complete lung collapse (collapse degree: 100%), controlled lung collapse (collapse degree: 90% and 50%) can better reduce the intraoperative lung injury, but there was no significant difference between the collapse degrees of 90 and 50%.

Introduction

One-lung ventilation (OLV) is a common ventilation method used in thoracic surgery (1). A traditional double-lumen endotracheal tube is widely used in thoracic surgery. In order to provide enough space for surgical operation, the application of complete lung collapse is recommended. This traditional ventilation method can cause an imbalance in ventilation flow, thereby increasing the amount of lung shunting and leading to hypoxemia (incidence rate of 9-27%) (2); and the secondary lung injury can occur. There are many studies on OLV, which are mostly limited by reducing lung injury via changing ventilation strategy or comparing the differences in lung injury caused by different lung isolation tools (3-5), but there is no study on the correlation between retaining the lung ventilation on operated side and lung injury. With the development of visual minimally-invasive technique of thoracic surgery, the prognosis of patients has attracted increased attention under the condition of completing the precision surgery (6,7). At the same time, the prognosis of patients has been paid more attention (8,9). In this study, a pulmonary sequestration tube device used to control the shunt in lung was developed (China

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patent: CN205073462 U) (10). which can control the degree of lung collapse during surgery while ensuing the surgical field; and the partial lung ventilation can be retained, so as to improve the prognosis of patients. From September 2015 to November 2016, the effects of complete lung collapse and controlled lung collapse on the pathology and physiology of lung were studied using the ventilator.

Materials and methods

Animals and materials. Eighteen experimental dogs of either gender were obtained from the Experimental Animal Center of Southern Medical University (Guangzhou, China). The mean animal weight was 9.5-15.5 kg. Before experimentation, the dogs were fasted for 12 h without water.

This study was approved by the Ethics Committee of Southern Medical University (Guangzhou, China).

Animal model preparation and grouping. After the peripheral veins were opened, 3% pentobarbital sodium (30 mg/kg, Sigma-Aldrich; Merck KGaA, Darmstadt, Germany), fentanyl (2 µg/kg, Yichang Renfu Pharmaceutical Co., Ltd.; Jiangxi, China) and cis-carbene sulfonate (0.1 mg/kg) (Jiangsu Sinobiopharma Co., Ltd., Jiangsu, China) were injected and the new single-lumen pulmonary sequestration tube was inserted. An anesthesia machine (Datex-Ohmeda, Inc., Madison, WI, USA) was used to control breathing. Sevoflurane was used to maintain anesthesia. The oxygen concentration (FiO_2) in the inhalation gas was 100%, tidal volume was 10-15 ml/kg, and respiratory rate was 12-16 times/min. A monitor (mindary BeneView T8 China) was used to monitor and maintain $PEtCO_2$ at 35-45 mmHg (1 kPa = 7.5 mmHg). During the experiment, the muscle relaxation was maintained via intravenous injection of cis-triptolulfonate. Limb electrocardiogram was monitored and a temperature probe was inserted at 5 cm into the anus to monitor rectal temperature. A blood oxygen saturation detection probe was placed on the tongue to monitor oxygen saturation. During the experiment, the rectal temperature was maintained at 37.5-38.5°C at room temperature of 24-26°C and humidity of 67-73%.

The femoral tube was dislocated to monitor the mean arterial pressure (MAP) and collect arterial blood. Femoral vein cannulation was performed to inject lactic acid Ringer's solution (8 ml·kg⁻¹·h⁻¹) using an infusion pump (Berenger, Berlin, Germany). A Swan-Ganz floating tube (Edwards Lifesciences, Irvine, CA, USA) was placed through right internal jugular vein. The tube was embedded in the pulmonary artery to monitor mean pulmonary arterial pressure (MPAP) and to collect mixed venous blood.

After the preparation of animal model, TLV was performed for 20 min and the dogs were randomly divided into 3 groups. The chest was opened between the fourth and fifth rib on the right side, and right lung collapse was induced. Left lung OLV was performed later. They were randomly divided into three groups according to the degree of right lung collapse with 6 dogs in each group: G1 group (100% collapse, complete right lung collapse), G2 group (90% collapse with 10% ventilation) and G3 group (50% collapse with 50% ventilation). The catheter used in each group was tested by aerodynamics at the factory, and the correspondence between the lumen throughput

Table I. Correspondence between lumen throughput of intra-
pulmonary shunting balance tube and intracapsular pressure in
tube wall (mean \pm SD) cmH ₂ O.

Tube no.	0% ventilation (G1)	10% ventilation (G2)	50% ventilation (G3)
1	30.4±1.1	24.8±2.1	18.8±3.0
2	28.7±0.8	23.1±3.1	18.0±2.5
3	29.4±1.2	22.6±1.0	17.5±1.7
4	24.1±0.3	19.5±2.4	15.6±1.8
5	25.7±0.9	20.1±1.7	17.8±1.7
6	27.4±0.4	22.8±0.6	16.2±1.4
7	29.5±1.3	22.2±1.5	17.8±1.5
8	31.4±0.4	25.7±1.9	19.4±2.4
9	28.7±1.0	23.4±1.6	17.7±2.9
10	35.1±1.3	27.4±0.8	21.8±1.5
11	30.5±2.1	24.1±0.9	19.8±2.2
12	33.0±2.2	26.0±3.9	22.3±2.2
13	27.8±1.9	21.8±2.0	19.7±1.9
14	32.3±1.1	27.6±1.5	23.2±2.1
15	30.0±0.9	24.8±2.7	18.8±2.6
16	26.3±1.5	22.4±3.4	17.0±3.4
17	28.1±1.9	21.6±2.4	18.1±1.7
18	26.9±0.6	20.4±1.1	17.4±1.2

Table II. Comparison of hemodynamic parameters among three groups of experimental dogs during OLV (mean \pm SD).

113±14	118±5	115±3
120±7	126±17	118±9
125±7	123±8	120±6
182±15	178±5	185±9
185±16	177±9	171±8
179±8	171±5	177±6
$2 20.0 \pm 3.9^{a}$	22.3±2.2ª	21.4 ± 2.5^{a}
9 17.8±2.0 ^{a,b}	9 19.7±1.9 ^{a,b}	20.5±2.2 ^{a,b}
1 16.0±1.5 ^{a,b}	20.2±2.1 ^{a,b}	21.5±1.8 ^{a,b}

^aP<0.05 compared with T0; ^bP<0.05 compared with G1 group.

and the minimum cuff pressure in the tube wall was measured (Table I). After OLV for 20 min, mixed venous blood and arterial blood were extracted from the femoral artery and jugular vein prior to TLV (T0), and at 30 (T1), 60 (T2), and 120 min (T3) after TLV for blood gas analysis (11-14). The remaining venous blood and arterial blood mixture was centrifuged (4°C, 2080 x g) for 12 min to collect the supernatant to quantify inflammatory factors. The supernatant was kept at -80°C

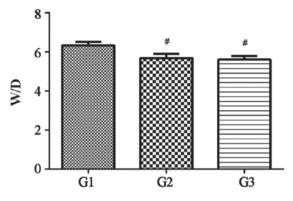


Figure 1. Effect of lung collapse degree on wet/dry ratio of lung (W/D). *P<0.05 compared with G1 group.

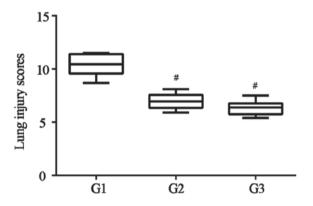


Figure 2. Effect of lung collapse degree on pathological score of lung tissues. *P<0.05 compared with G1 group.

before use. After OLV for 120 min, two small lung tissue pieces were collected from the ventilated side and the collapsed side, respectively. One lung tissue piece was used to determine W/D and the other piece was fixed in 10% formaldehyde solution for pathological examination.

Hemodynamic indicators. MAP, heart rate (HR) and MPAP were measured before blood sample collection for the comparison of hemodynamic stability.

Oxygenation indicators. Arterial blood was taken from the femoral artery at 20 min after TLV and at 30, 60 and 120 min after OLV. A Swan-Ganz tube was used to collect mixed venous blood. Blood gas analyzer (Nova Biomedical, Waltham, MA, USA) was used to measure the arterial partial pressure of oxygen (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂), oxygen saturation of arterial blood (SaO₂), partial pressure of oxygen in mixed venous blood (PvO₂), and mixed venous oxygen saturation (SvO₂). The pulmonary shunt rate was calculated according to the formula of the twocompartment model of pulmonary blood flow distribution: $Q_s/Q_t = (Cc'O_2-CaO_2)/(Cc'O_2-CvO_2) \times 100\%$, where Cc'O₂ is the blood oxygen content of pulmonary capillary.

Lung wet/dry weight ratio (W/D). After OLV for 20 min, the chest was opened and lung tissue was collected and washed with saline (4°C). Connective tissue was removed and filter paper was used to remove water on the surface. The tissue was

then placed in a clean and dry glass bottle, accurately weighed and baked in an oven at 75° C for 24 h to calculate the W/D and to assess the degree of lung tissue edema.

Detection of serum TNF- α and IL-6 levels via ELISA. Frozen serum was allowed to defrost completely. The TNF- α , ICAM-1 and IL-6 levels in serum were measured using ELISA kits according to manufacturer instructions.

Pathological examination of lung tissue. The middle lobe of the right lung was fixed in 10% neutral formaldehyde for 24 h, followed by dehydration and paraffin embedding. The tissue was cut into 4 μ m-thick sections which were stained via hematoxylin and eosin (H&E). The histopathological changes of lung tissues were observed under light microscope (Olympus, Tokyo, Japan) and scored according to four categories: i) alveolar hyperemia, ii) hemorrhaging, iii) alveolar or vascular wall neutrophil infiltration or aggregation, and iv) alveolar wall thickening and/or hyaline membrane formation. Scoring was performed on a 0-4 point scale according to the lesion severity; 0 point: no lesions or very mild lesions; 1 point: mild lesions; 2 points: moderate lesions; 3 points: severe lesions; 4 points: very severe lesions. The sum of all scores was taken as the total score of acute lung injury (ALI) (15).

Statistical analysis. Statistical Product and Service Solutions (SPSS) 19.0 software (IBM Corp., Armonk, NY, USA) was used for analysis, and measurement data were expressed as mean \pm SD; comparisons between groups were performed using ANOVA and the post hoc test was LSD test. P<0.05 indicates that the difference was statistically significant.

Results

Comparison of hemodynamic indexes. There were no significant differences in MAP and HR between groups at each time-point (P>0.05). MPAP of the G2 and G3 groups at T1, T2 and T3 were significantly lower than those in G1 group (P<0.05). No significant difference was found between G2 and G3 groups (P>0.05, Table II).

Oxygenation. Compared with the baseline values at T0, PaO_2 and PvO_2 were significantly decreased at all subsequent time-points (P<0.05). Qs/Qt was significantly increased (P<0.05), and changes in $PaCO_2$ levels were not significant (P>0.05). Compared with those in G1 group, the PaO_2 of G2 and G3 groups was significantly increased at T1, T2 and T3, while the Qs/Qt ratio was significantly decreased (P<0.05). There were no significant differences in $PaCO_2$ and PvO_2 between G1 and G2 or G3 groups at any time points (P>0.05, Table III).

Changes in serum TNF- α , ICAM-1 and IL-6 levels. Compared with the baseline values at T0, all three groups showed significantly increased TNF- α levels at T1, T2 and T3 (P<0.05). TNF- α levels in G2 and G3 groups were significantly lower at T1, T2 and T3 than those in G1 group (P<0.05) at the corresponding time-points. No significant difference in TNF- α level was found between G2 and G3 groups at any time-point (P>0.05). A similar pattern was observed regarding ICAM-1

Group	TO	T1	T2	Т3
PaCO ₂ (mmHg)				
G1	40.1±2.1	41.3±1.2	39.6±3.5	37.1±2.3
G2	38.3±3.4	40.6±2.8	42.3±2.0	39.4±3.1
G3	41.9±1.9	42.9±3.2	40.8±2.7	39.7±2.2
PaO ₂ (mmHg)				
G1	419.1±9.7	107.6±12.6 ^a	173.4±11.7ª	189.3±15.2ª
G2	426.2±17.2	158.9±13.8ª	237.0±18.3ª	258.6±20.2ª
G3	410.5±13.5	162.3±19.9ª	258.0±20.1ª	261.8±16.5ª
PvO_2 (mmHg)				
G1	60.1±2.5	44.9 ± 3.7^{a}	49.6±2.1ª	50.9±3.1ª
G2	64.8±1.8	51.3±2.6ª	55.0±2.8ª	54.3 ± 2.7^{a}
G3	62.2±2.1	53.7±2.8ª	54.8±1.1ª	53.6±1.6ª
Qs/Qt (%)				
G1	19.2±2.2	47.7 ± 1.9^{a}	40.2 ± 4.0^{a}	38.7±3.5ª
G2	20.3±3.1	$40.1 \pm 2.3^{a,b}$	35.1±3.1 ^{a,b}	32.1±1.6 ^{a,b}
G3	18.0±1.6	$39.2 \pm 1.5^{a,b}$	32.9±2.3 ^{a,b}	$30.4 \pm 2.8^{a,b}$

Table III. Comparison of oxygenation indexes among three groups of experimental dogs during OLV (mean ± SD).

^aP<0.05 compared with T0; ^bP<0.05 compared with G1 group.

Table IV. Comparison of the effect of lung collapse degree on inflammatory indexes in mixed arterial and venous blood (mean \pm SD).

Inflammatory index	Group	T0	T1	T2	T3
TNF-α (pg/ml)	G1	0.32±0.10	6.84±1.12ª	8.28±1.07ª	8.64±1.12 ^a
	G2	0.38±0.10	5.07±1.21 ^{a,b}	5.88±0.68 ^{a,b}	5.13±0.63 ^{a,b}
	G3	0.31±0.14	$3.18 \pm 1.00^{a,b}$	$4.61 \pm 0.67^{a,b}$	4.56±1.35 ^{a,b}
ICAM-1 (ng/ml)	G1	7.14±1.05	20.45±0.96ª	30.81±1.04ª	36.33±0.60ª
-	G2	7.21±1.24	15.74±1.44 ^{a,b}	18.57±0.46 ^{a,b}	20.00±0.65 ^{a,b}
	G3	7.51±1.20	$9.92 \pm 0.98^{a,b}$	13.45±0.53 ^{a,b}	14.62±0.43 ^{a,b}
IL-6 (pg/ml)	G1	4.62±1.59	63.36±6.42ª	66.08±7.04ª	54.07±5.29ª
	G2	5.06±1.50	$20.39 \pm 5.04^{a,b}$	26.62±3.96 ^{a,b}	22.49±4.45 ^{a,b}
	G3	5.67±1.84	19.71±3.98 ^{a,b}	28.19±3.13 ^{a,b}	20.29±3.75 ^{a,b}

and IL-6 levels. Compared with the baseline values at T0, ICAM-1 and IL-6 levels were significantly increased at T1, T2 and T3 (P<0.05). ICAM-1 and IL-6 levels in G2 and G3 groups were significantly lower at T1, T2 and T3 than those in G1 group (P<0.05) at the corresponding time points. No significant differences in ICAM-1 and IL-6 levels were found between G2

Lung W/D. W/D of lung in each group was as follows: G1 group: 6.33 ± 0.55 ; G2 group: 5.69 ± 0.67 ; G3 group: 5.61 ± 0.56 . W/D was significantly decreased in G2 and G3 groups compared with that in G1 group (P<0.05). No significant difference was found in W/D between G2 group and G3 group (P>0.05, Fig. 1).

and G3 groups at any time point (P>0.05, Table IV).

Histopathological examination of lung tissues. The pathological examination of the collapsed side (right lung) was as follows: The G1 group showed significant changes in alveolar wall edema, pulmonary interstitial thickening, vascular congestion, serious inflammatory cell infiltration and alveolar structure damage. The alveolar structures of G2 and G3 groups were better than that in G1 group; the pulmonary interstitial and alveolar cavity exudates and inflammatory cell infiltration were significantly reduced compared with those in G1 group (Figs. 2 and 3).

ALI score in each group: G1 group: 10.33 ± 0.98 points; G2 group: 6.99 ± 0.73 points; G3 group: 6.34 ± 0.68 points. Compared with that in G1 group, the ALI scores of G2 and G3 groups were significantly reduced (P<0.05). There was no

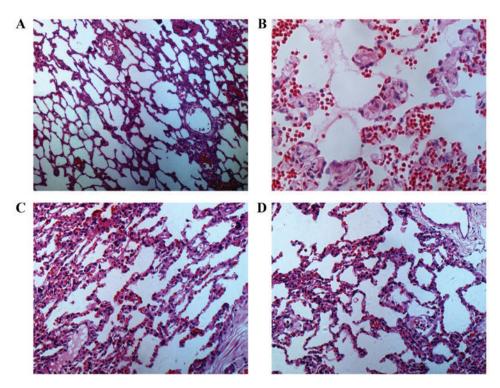


Figure 3. Effect of lung collapse degree on pathological changes of lung tissues (H&E, x400 magnification). (A) G1 group; (B) G1 group; (C) G2 group; (D) G3 group.

significant difference in ALI score between G2 and G3 groups (P>0.05).

Discussion

OLV is a common ventilation method used in thoracic surgery. The lumen diameter of the traditional double-lumen tube is large and can cause damage to the glottis, throat edema and postoperative hoarseness. After intubation tube, the bronchofiberscope should be disconnected; otherwise, the displacement or dislocation may occur when the position is adjusted. During tube application, the lung is in a collapsed state. Although it is beneficial for surgical operation, OLV can cause lung collapse, which in turn leads to increased intrahepatic shunt, hypoxia and high airway pressure in the healthy lung, causing different degrees of lung injury later (16,17). In this study, the controlled lung collapse based on the previous study on lung injury was proposed for the first time. The tube of controlling the shunt in the lung used in this study was characterized by thinner lumen, thus effectively reducing the airway damage. The size of sealing elements in the bronchial cavity can be controlled by controlling intake air volume combined with a pressure gauge to monitor internal pressure, which in turn controls the collapse degree on the surgical side of lung while ensuring the good surgical field. The ventilation on the surgical side of lung can improve the re-expansion pulmonary edema and secondary acute lung injury of patients during surgery, and improve oxygenation and hemodynamic status of patients. The lower end of tracheal catheter is porous and open, which needs no para-ventilation under general anesthesia. The intubation has a high success rate, no need for bronchofiberscope and large air flow, which can improve oxygenation and control the intraoperative ventilation of patients more precisely. It breaks through the traditional anesthesia method of complete lung collapse on the operated side, and reduce the damage of intubation tube to the bronchus. In particular, it can also improve the quality of oxygenation and prognosis of patients with chronic bronchitis and emphysema.

In this study, we found that PaO₂ was significantly decreased while Qs/Qt was significantly increased (18) at 30 min during early-stage OLV due to no ventilation, the presence of blood flow in the collapsed lung and increased pulmonary shunting. PaO2 was gradually increased while Qs/Qt was gradually decreased at 1 h after OLV, possibly due to the hypoxic pulmonary vasoconstriction (HPV) response that causes lateral pulmonary artery contraction on the collapsed side and increases the pulmonary vascular resistance. With these changes, the blood flow is transferred to the ventral side of lung, thereby improving the imbalanced ventilation/perfusion ratio, reducing pulmonary shunting, and maintaining normal PaO₂ (19). In this study, the retention of partial alveolar ventilation in the experimental group significantly improved the shunt rate. At 1 h after OLV, the pulmonary shunting was significantly better than that in $\tau \eta \epsilon$ complete collapse group, and the oxygenation condition was also significantly improved.

The overexpansion of alveoli during mechanical ventilation and the shear stress produced by repeated opening and closing, as well as local lung collapse can induce lung inflammatory responses and cause inflammation cascade initiation (20,21). Pulmonary shunting, high airway pressure, lung ischemia-reperfusion injury and ventilation imbalance can damage alveolar capillary endothelium and stimulate alveolar macrophages to release a large number of proinflammatory mediators (22). Among the proinflammatory mediators, TNF- α has anti-infection and immune regulation functions, and it is one of the most important mediators of early state inflammation, as it can induce other inflammatory mediators and initiate inflammatory cascade reactions. ICAM-1 is an important immunoinflammatory molecule that mediates the adhesion reaction, which plays an important role in promoting the adhesion of inflammatory site, controlling tumor deterioration and metastasis and regulating the immune response. The expression of ICAM-1 is important to the degree of tissue injurv. IL-6 is the strongest inflammatory mediator of the proinflammatory cytokines, which is associated with the severity and duration of tissue damage and can reflect the severity of inflammatory responses due to surgical stress. In this study, controlled lung collapse and partial ventilation significantly improved lung injury degree during operation. TNF-a, ICAM-1 and IL-6 levels were gradually increased over time in G1 group with complete lung collapse, indicating that OLV causes immune inflammatory response and lung injury. However, TTNF-α, ICAM-1 and IL-6 levels in G2 and G3 groups were significantly lower than those in G1 group, suggesting that partial ventilation of the collapsed lung can reduce the severity of immune inflammatory reactions and protect lung tissue to a certain extent, improving prognosis and accelerating postoperative recovery.

Due to the imbalance of ventilation/perfusion ratio in OLV, hypoxemia is caused, triggering the production the release of a large number of inflammatory mediators, increasing the pulmonary capillary permeability (23) and increasing the lung water content on the collapsed side, ultimately leading to acute lung injury (ALI). The main pathological changes are extensive pulmonary inflammation, neutrophil aggregation, pulmonary interstitial edema, damaged pulmonary capillary endothelial cell, alveolar epithelial cell integrity, and penetration of protein-rich fluids into alveolar cavities. In this study, at 2 h after complete lung collapse, the dogs in G1 group showed significant hypoxemia, pulmonary edema and lipid peroxidation. Through pathological observation, alveolar wall edema, pulmonary interstitial thickening and serious inflammatory cell infiltration in alveolar cavities, and damaged alveolar structure were found. Our experiment successfully proved that the partial retention of collapsed lung ventilation can significantly improve oxygenation, reduce W/D of lung tissues and decrease plasma inflammatory factor levels without affecting the visual field. These results suggest that the controlled lung collapse can alleviate acute lung injury in experimental dogs to a certain extent.

In this study, the physiological indicators and inflammatory indicators in G2 and G3 groups were very similar, and there were usually no statistically significant differences in statistical analysis. The reasons may be that the current data measured are insufficient to produce the statistically significant differences due to the small sample size, so it is needed to further increase the sample size. In addition, there was partial alveolar ventilation in the two groups, but the maximum experimental time was set to only 2 h, so there was no significant difference yet due to the short time. Therefore, the time and sample size should be increased for further study.

In this study, we confirmed that a new type of lung sequestration tube can control the degree of lung collapse during OLV in thoracotomy. The partial retention of collapsed lung ventilation can significantly improve the intraoperative oxygenation, thereby reducing lung injury caused by OLV during surgery without affecting the visual field. Further studies are still needed to explore whether this new type of tube can reduce the burden on other organs when used to protect the lung.

Acknowledgements

Not applicable.

Funding

This study was supported by Guangdong Province Science and Technology Planning projects: 00174990166341080, 2016B090918111, 701253476268, 2014A020212583 and Horizontal fund project (SZLB201218) (SZMR20120918) (JSLY20130118), China patent number ZL2015 2.0247672.2; ZL2017 3 0099023 7; ZL2017 3 0098968.7.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GL, HW and XLu analyzed and interpreted the patient data, and GL drafted the manuscript. XM, MX, PX, MY and XuY performed the experiment and participated in the design of the study. YW, XiY and AZ participated in the analysis and discussion of the data. RL and JT were responsible for the collection of the data and the follow-up management of the patients. XLi and YZ were responsible for the statistical analysis of the data. JX was devoted to designing the methods and revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Southern Medical University (Guangzhou, China).

Patient consent for publication

Not applicable.

Competing interests

Two authors of this study (JX and MX) are among the inventors of the patent CN205073462. According to Article 24 of the Intellectual Property Law of People's Republic of China and Article 60 of Chapter VII of the Patent Law of the People's Republic of China, the patent holders have permitted the authors to use the pulmonary sequestration tube device described in this patent, where the use is limited to projects for non-profit research.

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