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Effect of protective ventilation on pro-inflammatory cytokine response during one lung ventilation in esophagectomy: a randomized controlled study

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Abstract

Background: Esophagectomy is associated with increase in pro-inflammatory cytokine whose extent has been claimed as a causative agent of postoperative acute lung injury.

Objectives: The aim of this study was to determine whether a ventilatory strategy based on the reduction of tidal volume (V_T) and a moderate level of positive end-expiratory pressure (PEEP) during one lung ventilation (OLV) could reduce the pro-inflammatory cytokine response associated with esophagectomy. Also, its impact on oxygenation and postoperative outcome were evaluated.

Patients and methods: Thirty patients were randomly allocated into two groups**:** Group (CV), Patients (n = 15) received a conventional ventilation strategy (tidal volume of 9 ml/kg during two-lung and OLV); no PEEP was applied and group (PV), Patients (n = 15) received a protective ventilation strategy (tidal volume of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during OLV and PEEP 5 cm H_20 was applied. Serum level of interleukins (IL-6 and IL-8) were measured at baseline time after anesthetic induction ($T_{Baseline,}$); at the end of abdominal stage of the operation ($T_{Abdo,}$); at the end of OLV ($T_{OLV\ end,}$); 1 hour and 20 hour after The end of the surgical procedure respectively ($T_{Postop1}$) and ($T_{Postop20,}$). Also, peri-operative oxygenation and post-operative outcome were evaluated.

Results: There were significant increases in blood level of IL-6 and IL-8 all over the time in both groups in comparison to their baseline values (p= 0.001). However there were significant reduction in blood level of IL-6 and IL-8 in group PV compared to CV group all over the study period (p<0.05)**.** The oxygenation index was significantly higher in PV group during the period of OLV (p< 0.001) and during the first day postoperatively (p< 0.001)**.** There was no significant difference in post-operative outcome between groups.

Conclusion: The use of V_T 5 ml /kg and PEEP of 5 cm H_2O during OLV reduced the systemic pro-inflammatory cytokine response, improved peri-operative oxygenation, but there were no significant differences in occurrence of ARDS or postoperative outcome in patients undergoing esophagectomy.

Introduction

There are multiple factors in the surgical environment which can contribute to lung injury. The most obvious is the surgical approach. Site of operation is an important predictor of pulmonary complications, with upper abdominal and thoracic incisions being the most important [1].

Previous studies have identified the use of large tidal volumes as a major risk factor for the development of lung injury in mechanically ventilated patients without acute lung injury (ALI). Gajic reported that 25% of patients with normal lungs who were ventilated in an intensive care unit (ICU) setting for two days or longer developed (ALI) or acute respiratory distress syndrome (ARDS) [2]. The main risk factors for ALI were use of large tidal volumes, restrictive lung disease and blood product transfusion. A prospective study from the same group found that tidal volumes > 700 ml and peak airway pressures (P peak) > 30 cmH2O were independently associated with the development of ARDS [3].

The current anesthetic practice in esophagectomy is one lung ventilation (OLV) to facilitate surgical exposure. Anesthesiologists are accustomed to give the same tidal volume (V_T) during OLV to avoid atelectasis and hypoxemia but this was associated with marked increase in pro-inflammatory cytokines [3].

The pro-inflammatory cytokines are released in part from lung during isolation and in the other part from extensive tissue destruction, the combination of both factors acts synergistically to cause the changes of the immune response [4].

Previous studies used small V_T and 5 cm H_2O positive end expiratory pressure (PEEP) found decreased release of pro-inflammatory cytokines without adverse effects [4]. In patients with normal lungs, two studies have suggested that applying PEEP and reducing V_T did not influence plasma cytokine release during mechanical ventilation for elective surgery [5, 6].

The aim of this study was to determine whether a ventilatory strategy based on the reduction of V_T during OLV and a moderate level of PEEP during OLV could reduce the pro-inflammatory cytokine response associated with esophagectomy. Also, detect its impact on oxygenation and postoperative outcome.

Patients and Methods

This randomized prospective study was approved by the local ethics committee of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

After written informed consent 30 patients ASA 1 and II, (age, 20-60 years) scheduled for elective Ivor Lewis esophagectomy were enrolled in this study.

Patients with New York Heart Association (NYHA) class III or IV, preexisting chronic obstructive pulmonary disease with forced expiratory volume in 1 second (FEV1) of less than 80% of predicted and/or (FEV1) over forced vital capacity (FVC) ratio of less than 0.7, chronic renal failure (serum creatinine > 2 mg/dl), altered liver function (Child-Pugh class B or more) were excluded from this study.

The night before surgery, oral diazepam 10 mg and ranitidine 50 mg were given. Upon arrival at the operating room, peripheral venous line, subclavian vein and radial artery catheters were established. Lactated ringer،s solution 10 ml\kg was infused 10 minutes before the initiation of anesthesia. Monitoring probes (ECG, invasive blood pressure, pulse oximeter and temperature) were applied.

Patients were randomly allocated into two groups CV &PV (each consists of 15 patients) by using opaque sealed envelopes containing computer generated randomization schedule, the opaque sealed envelopes are sequentially numbered that were open before application of anesthetic plan.

Group (CV)

Patients received a conventional ventilation strategy (tidal volume of 9 ml/kg during two-lung and one-lung ventilation); no positive end-expiratory pressure (PEEP) was applied.

Group (PV)

Patients received a protective ventilation strategy (tidal volume of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation and positive end-expiratory pressure 5 cm H_20 was applied.

General anesthesia was induced by I.V Fentanyl 2 µg/kg, Propofol 1-2 mg /kg. Tracheal intubation was facilitated by Cisatracurium 0.15 mg / kg, a double-lumen tube was inserted, and then, general anesthesia was maintained with Isoflurane and Cisatracurium 0.03 mg/kg every 30 min.

The respiratory rate was adjusted to keep end tidal carbon dioxide ($ETCO_2$) between 35 and 45 mmHg throughout anesthesia. The initial inspired oxygen fraction (FIO_2) was 0.5 using oxygen-and-air mixture and was increased if necessary to keep SPO_2 greater than 90%. In case of peri-operative hypoxemia, the only treatment used was an increase in (FIO_2). Heart rate , mean arterial blood pressure (MAP), oxygenation index (OI) =PO_2/FIO_2, $PaCO_2$, peak inspiratory pressure (P peak) and plateau pressure (P plateau) obtained at, baseline time after anesthetic induction ($T_{Baseline,}$); at the end of abdominal stage of the operation ($T_{Abdo,}$); 15 min after initiation and at the end of OLV, ($T_{OLV\ 15}$)and ($T_{OLV\ end,}$) respectively. Duration of surgery, transfusion requirement, and urine output were recorded.

Surgical procedures included, first, a median laparotomy with construction of a neoesophagus using the stomach and, second, a right thoracotomy in lateral decubitus position allowing subtotal esophagectomy combined with two fields lymphadenectomy and esophagogastric anastomosis through the thoracic route.

At the end of the operation patients were transferred to post anesthesia care unit (PACU) and were monitored with ECG, invasive blood pressure and pulse oximeter. CVP was measured every 2 hours. Urine output, surgical drains and intercostal tubes were observed and calculated. ABG analysis was done every 12 hour and chest x-ray every 24 hour.

Postoperative analgesia comprised patient-controlled analgesia (PCA) with an initial morphine bolus of 0.1mg/kg once pain was expressed by the patient or if VAS ≥ 3, followed by 1 mg boluses with a lockout period of 5 minutes. The patients were followed up in their stay in PACU for detection of any post-operative complications.

Measurement of interleukin (IL), IL-6 and IL-8

Five samples of venous blood were obtained for measurement of interleukin (IL), IL-6 and IL-8 at, $T_{Baseline,}$, $T_{Abdo,}$, $T_{OLV\ end}$, $T_{Postop1}$ and $T_{Postop20}$, 1 and 20 hr after The end of the surgical procedure respectively.

Blood samples were collected into non pyrogenic, sterile falcon tubes. Serum was separated by cold centrifugation of the blood at 1,500*g* for 10 min and stored at -70°C. To improve the homogeneity of measurements, all of the samples were analyzed at the same time with the same assay reagents by the same laboratory technician blinded to the groups. Serum IL-6 and IL-8 were measured using enzyme- linked immunosorbent assay (human IL-6 and IL-8 ELISA KIT, AVIBION, Ani Biotech oy, Finland. The lower detection limits for these kits are 7 pg/ml and 2 pg/ml, respectively.

Statistical analysis:

Data analysis was done using SPSS version 20 (Statistical package for social science). The minimal requirement for the calculated sample size was 11 patients per group to detect a difference in mean IL-6 concentration of 33%, an estimated SD of 79.5%, with a power of 80% and a 5% risk of type I error. Qualitative data was described by numbers and percentages, where quantitative data was described using mean and standard deviation. Chi-square test was used to test relation between qualitative variables where independent samples T-test was used to compare between two groups of quantitative data. $p < 0.05$ was considered significant.

Results

There were no significant differences among the two groups in demographic data, patients characteristics and intra operative data (p>0.05) (table 1, 2).

In the PV group, there were significant decrease in P peak and P plateau during the period of OLV ($T_{OLV\ 15}$ and $T_{OLV\ END}$) (p>0.05) (table 3).

Although $PaCO_2$ was significantly increased in the PV group compared with CV group at OLV ($T_{OLV\ 15}$ and $T_{OLV\ END}$) (p<0.001) it was in safe limits (table 3). Also, there was significant decrease in (PH) in the PV group compared with CV group during period of OLV ($T_{OLV\ 15}$ and $T_{OLV\ END}$) in comparison to their baseline values (p< 0.001) (table 3).

The oxygenation index was significantly better in PV group during the period of OLV (p< 0.001) and during the first day postoperatively (p< 0.001) (Fig.1).

Analysis of variance revealed that there were significant increases in serum levels of IL-6 and IL-8 all over the time in both groups in comparison to their baseline values (p= 0.001), however there were significant reduction in blood level of IL-6 and IL-8 in group PV group compared to CV group all over the study period (p<0.05) (Fig. 2, 3).

Eight patients (53.3%) in CV group and six patients (40%) in PV group exhibited pneumonia. pleural effusion developed in 6 patients (40%) in CV group and 4 patients (26.7%) in PV group. One patient (6.7%) in CV group had pneumothorax. ARDS developed in 3 patients (20%) in CV group and 2 patients (13.3%) in PV group.

Arrhythmia developed in 4 patients (26.7%) in CV group and 4 patients (26.7%) in PV group with no significant difference in the incidence of post-operative adverse effects noted between 2 groups (P>0.05) (table 4).

Postoperative mortality occurred in 6 patients (40%) in CV group and 4 patients (26.7) in PV group.

There was no significant difference in the duration of stay in PACU among the two groups (P= 0.132) (table 4).

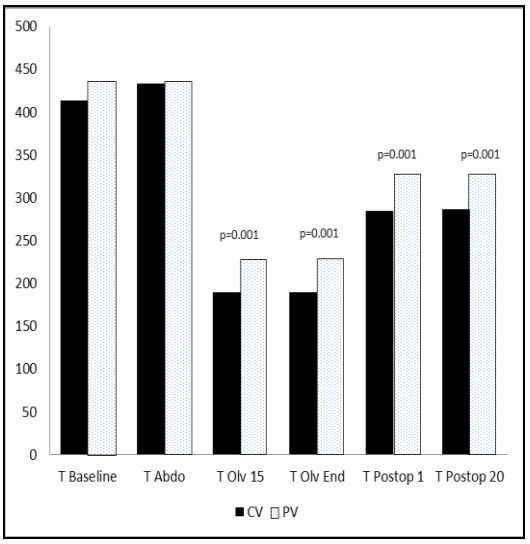

Fig. (1) Oxygenation index

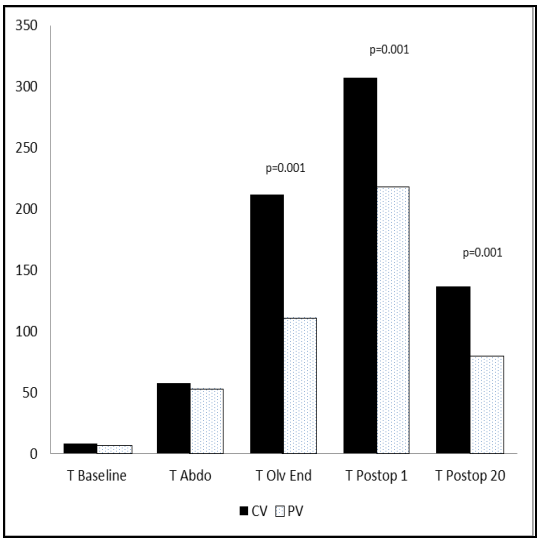

Fig. (2) Interleukin 6

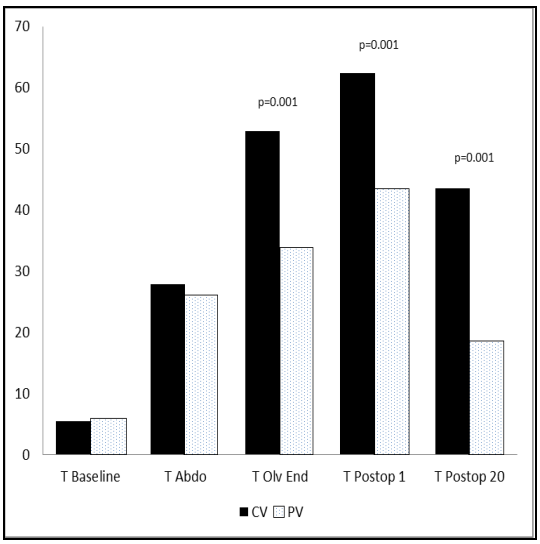

Fig. (3) Interleukin 8

Table 1: Demographic data and patients characteristics

	CV (n=15)	PV(n=15)	P. value
Age, yr	56.3 ± 9.9	59.2 ± 6.5	0.382
SEX, M/F	11/4	11/4	0.659
BMI, kg/m²	22.5 ± 2.9	22.1 ± 3.3	0.688
ASA, n(%)			
I	9(60.0)	8(53.3)	0.501
II	6(40.0)	7(46.7)	
NYHA, n(%)			
I	10(66.7)	9(60.0)	0.501
II	5(33.3)	6(40.0)	
FEVI / FVC, Mean±SD	83.7 ± 4.6	84.3 ± 4	0.721
Po2, Mean±SD	80.7 ± 5.6	83.1 ± 4.2	0.158
DM, n(%)			
Yes	7(46.7)	9(60.0)	0.358
No	8(53.3)	6(40.0)	
Pre op albumin, n(%)			
3 - 3.5	11(73.3)	8(53.3)	
3.5 - 4	3(20.0)	7(46.7)	0.215
>4	1(6.7)	0(0.0)	
Pre op HB, n(%)			
10 - 12	11(73.3)	10(66.7)	
12 - 14	3(20.0)	5(33.3)	0.461
>14	1(6.7)	0(0)	
Dysphagia, n(%)			
Yes	12(50.0)	11(73.3)	0.501
No	3(20.0)	4(26.7)	
Tumor histology, n(%)			
Adenocarcinoma	13(86.7)	11(73.3)	
Squamous cell carcinoma	2(13.3)	4(26.7)	0.326

CV: conventional ventilation. PV: protective ventilation. BMI: body mass index. ASA: American society of anesthesiologists. NYHA: New York heart association. FEV1: forced expiratory volume in one second. FVC: forced vital capacity.Pao2: partial pressure of oxygen tension. D.M: diabetes mellitus.

Table 2: Intra-operative data

	CV	PV	P. value
Surgery duration(min)	269.3 ± 20.6	269 ± 20.9	0.965
One lung ventilation duration (min)	91 ± 17.2	90.7 ± 16.7	0.958
Mechanical ventilation duration(min)	288.7 ± 18.2	287.7 ±16.5	0.875
Blood Loss (ml)	660 ± 276.6	680 ± 260.4	0.840
blood Transfusion (ml)	860 ± 331.2	853.3 ± 313.7	0.956
Fluid administration (ml)	2466.7 ± 639.9	2540 ± 581.6	0.744
Urine output (ml)	356 ± 105.4	374.7 ± 89.3	0.657

CV: conventional ventilation. PV: protective ventilation.

Table (3): Respiratory and hemodynamic variables

	T Baseline		T Abdo		T Olv 15		T Olv End	
	CV	PV	CV	PV	CV	PV	CV	PV
P peak	18± 2	18.1± 1.9	19±3	18±2	35±4	26.1+3*	36±2	27±3*
P plat	14±3	14.1±2	13.5±2	13±2	27±3	20±2*	28±2	21±2*
Paco2	39±5	39.1±4	38± 2	38.1± 3	42±2	47+3*	43±3	48.2±4*
PH	7.43±0.04	7.42±0.04	7.42± 0.04	7.41± 0.02	7.35±0.01	7.33±0.02*	7.36±0.02	7.33±0.03*
MAP	80± 10	79± 12	78± 10	77± 11	76±8	71±10	77±10	72±11
HR	65±12	66±11	67± 13	68± 10	79±11	75±13	84±13	77±14

CV: conventional ventilation. PV: protective ventilation. RR: respiratory rate. VT: tidal volume. P peak: peak airway pressure. P plat: plateau pressure. Paco2: partial arterial carbon dioxide tension. MAP: mean blood pressure. HR: heart rate.* Significant difference at p. value<0.05 in comparison with baseline values.

Table (4): outcome of patients

	CV		PV		P. value
	No.	%	No.	%	
Pneumonia	8	53.3	6	40.0	0.357
Pleural effusion	6	40.0	4	26.7	0.349
Pneumothorax	1	6.7	0	0.0	0.501
ARDS	3	20.0	2	13.3	0.501
Arryrhmia	4	26.7	4	26.7	0.339
Anastomotic leak	6	40.0	4	26.7	0.349
Surgical reintervention	2	13.3	0	0.0	0.232
Myocardial Ischaemia	1	6.7	2	13.3	0.501
Septic shock	3	20.0	2	13.3	0.501
Renal failure	3	20.0	2	13.3	0.501
PACU duration (Mean $\pm$ SD)	17 ± 4		15 ± 3		0.132
Post- operative mortality	6	40.0	4	26.7	0.349

CV: conventional ventilation. PV: protective ventilation.

Discussion

Clinical studies suggest that mechanical ventilation can modify inflammatory response in patients with acute lung injury. Other few studies addressed the effects of mechanical ventilation using a high V_T strategy on pulmonary inflammatory response in patients without lung disease mostly during major surgery [4,5,7,8,9].The present study has shown that the use of V_T 5 ml /kg and PEEP of 5cm H_2O during OLV reduced the systemic pro-inflammatory response, improved oxygenation, decreased the P peak and P plateau during the period of OLV but there were no significant differences in occurrence of ARDS or postoperative outcome between groups.

Several studies have evaluated the impact of ventilatory strategies on inflammatory response and pulmonary function during major surgery [5,6,9]. In contrast to our findings, their results indicated that mechanical ventilation with high V_T and no PEEP did not result in higher cytokine levels when compared to strategies including a reduction of V_T associated with PEEP during major surgical procedures.

A study of patients having esophageal surgery compared the use of tidal volumes of 9 ml / kg without PEEP during two and one lung ventilation (OLV) vs. 9 ml / kg during two-lung ventilation and 5 ml / kg during OLV with PEEP of 5 cm H_2O during all the operative time [4]. They found significant lower serum markers of inflammation [interleukin (IL)-b, IL-6, and IL-8] in the lower tidal volume plus PEEP group. The study demonstrated better oxygenation in the lower tidal volume group during and immediately after OLV, with earlier extubation (post-operative mechanical ventilation duration, 115 vs. 171 min).

Esophagectomy required left OLV, which, although limited in time, has been reported to promote ventilation-induced lung injury in both experimental and clinical settings with similar duration [10]. Although the exclusion of one lung and the use of OLV should theoretically include a reduction of V_T to 5 ml/kg, the hypothetic risk of derecruitment and hypoventilation frequently promotes the maintenance of the same level as during two-lung ventilation without PEEP [11,12]. This type of mechanical ventilation may lead to over distension of the remaining aerated lung regions and increase the shear forces generated during repetitive opening and collapse of atelectatic areas [10,13]. Furthermore, during OLV in lateral decubitus, the compression atelectasis of dependent lung regions, the loss of elastic recoil after thoracotomy, and mediastinal surgical manipulations can markedly reduce the aerated lung capacity, impair ventilation distribution, and worsen ventilation/perfusion mismatch [14,15,16].

Ventilator induced lung injury (VILI) involves a complex interaction of over distension (volutrauma), increased trans-pulmonary pressure (barotrauma), cyclic opening and closing of alveoli (atelectotrauma), and inflammatory mediators (biotrauma) [13]. This interaction involves the alveolar epithelium, vascular endothelium, polymorphonuclear leukocyte (PMN) recruitment and activation, and apoptosis/necrosis balance. Mechanotransduction is the key link between the physical forces (such as stress and strain) imposed on the lung and intracellular signaling pathways leading to the production of cytokines.

Recent studies have demonstrated the clinical relevance of the pro-inflammatory cytokine response in the postoperative course of esophagectomy as predictive of cardiac or pulmonary complications such as acute respiratory distress syndrome [17,18,19]. The prolonged half-life of IL-6 and the related ease of detecting circulating level has made this cytokine a precious indicator of both duration and extent of surgical injury [17,20,21].

Moreover, because IL-6 seems to be a good marker of ventilator-induced injury [22].It was chosen as the most reliable marker of the peri-operative pro-inflammatory response in the studied setting. Also, IL-8 is one of the most important cytokines responsible for the recruitment of inflammatory cells to the alveoli. It is increased in the broncho-alveolar lavage fluid (BAL) of patients with ARDS, sepsis, and multi-organ failure [20].

Our results have not demonstrated significant difference between groups in the post-operative outcome. However, this study was not powered for clinical endpoints, and further studies should be performed to assess the influence of such a strategy on clinical outcomes.

Study limitations:

Potential limitations worth consideration include the small number of patients studied in a single institution, limiting the generalizability of the conclusions.

Conclusion

Our study concluded that the use of V_T 5 ml /kg and PEEP of 5cm H_2O during OLV reduced the systemic pro-inflammatory response, improved oxygenation, decreased the P peak and P plateau during the period of OLV but there were no significant differences in occurrence of ARDS or postoperative outcome in patients undergoing esophagectomy.

References

[1] Smetana GW: **Postoperative pulmonary complications: an update on risk assessment and reduction.** *Cleve Clin J Med* 2009, **76** (Suppl 4):60-65.

[2] Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD: **Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation.** *Crit Care Med* 2004, **32**:1817-1824.

[3] Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A: **Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patints**. *Intensive Care Med* 2005, **31**:922-926.

[4] Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray JP. **Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study.** *Anesthesiology* 2006, **105**:911-919.

[5] Wrigge H, Zinserling J, Stuber F, von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C: **Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function.** *Anesthesiology* 2000, **93**:1413–1417.

[6] Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C: **The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery.** *Anesth Analg* 2004, **98**:775–781.

[7] Wrigge H, Uhlig U, Baumgarten G, Menzenbach J, Zinserling J, Ernst M, Dromann D, Welz A, Uhlig S, Putensen C: **Mechanical ventilation strategies and inflammatory responses to cardiac surgery: a prospective randomized clinical trial.** *Intensive Care Med* 2005, **31**:1379-1387.

[8] Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, Ranieri VM: **Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial.** *J Thorac Cardiovasc Surg* 2005, **130**:378-383.

[9] Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N: **Effects of Protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass.** *Intensive Care Med* 2004, **30**:620-626.

[10] Gama de Abreu M, Heintz M, Heller A, Sze´chenyi R, Albrecht D, Koch T: **One-lung ventilation with high tidal volumes and zero positive end-expiratory pressure is injurious in the isolated rabbit lung model.** *Anesth Analg* 2003, **96**:220–228.

[11] Benumof J: **Conventional and differential lung management of one-lung ventilation, Anesthesia for Thoracic Surgery**, 2nd edition. Philadelphia, Saunders; 1994, 413–424.

[12] Brodsky J, Fitzmaurice B: **Modern anesthetic techniques for thoracic operations.** *World J Surg* 2001, 25:162–166.

[13] Parker J, Hernandez L, Peevy K: **Mechanisms of ventilator-induced lung injury.** *Crit Care Med* 1993, **21**:131–143.

[14] Brismar B, Hedenstierna G, Lundquist H, Strandberg A, Svensson L, Tokics L: **Pulmonary densities during anesthesia with muscular relaxation, a proposal of atelectasis.** *Anesthesiology* 1985, **62**:422–428.

[15] Hedenstierna G, Tokics L, Strandberg A, Lundquist H, Brismar B: **Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis**. *Acta Anaesthesiol Scand* 1986, **30**:183–191.

[16] Klingstedt C, Hedenstierna G, Baehrendtz S, Lundqvist H, Strandberg A, Tokics L, Brismar B: **Ventilation-perfusion relationships and atelectasis formation in the supine and lateral positions during conventional mechanical and differential ventilation.** *Acta Anaesthesiol Scand* 1990, **34**:421–429.

[17] Kooguchi K, Kobayashi A, Kitamura Y, Ueno H, Urata Y, Onodera H, Hashimoto S: **Elevated expression of inducible nitric oxide synthase and inflammatory cytokines in the alveolar macrophages after esophagectomy.** *Crit Care Med* 2002, **30**:71–76.

[18] Abe T, Oka M, Tangoku A, Hayashi H, Yamamoto K, Yahara N, Morita K, Tabata T, Ohmoto Y: **Interleukin-6 production in lung tissue after transthoracic esophagectomy.** *J Am Coll Surg* 2001, **192**:322–329.

[19] Tsukada K, Hasegawa T, Miyazaki T, Katoh H, Yoshikawa M, Masuda N, Kuwano H: **Predictive value of interleukin-8 and granulocyte elastase in pulmonary complication after esophagectomy**. *Am J Surg* 2001, **181**:167–171.

[20] Nakazawa K, Narumi Y, Ishikawa S, Yokoyama K, Nishikage T, Nagai K, Kawano T, Makita K: **Effect of prostanglandine E1 on inflammatory responses and gas exchange in patients undergoing surgery for oesophageal cancer.** *Br J Anaesth* 2004, **93**:199–203.

[21] Yamada T, Hisanaga M, Nakajima Y, Kanehiro H, Watanabe A, Ohyama T, Nishio K, Sho M, Nagao M, Harada A, Matsushima K, Nakano H: **Serum interleukin- 6, interleukin-8, hepatocyte growth factor and nitric oxide changes during thoracic surgery**. *World J Surg* 1998, **22**:783–790.

[22] von Bethmann A, Brasch F, Nusing R, Vogt K, Volk H, Muller K, Wendel A, Uhlig S: **Hyperventilation induces release of cytokines from perfused mouse lung.** *Am J Respir Crit Care Med* 1998, **157**:263–272.