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Research Article

Can Ventilator Settings Influence Lung Damage Biomarkers KL-6 and CRP during One Lung Ventilation?

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ABSTRACT

Background: Volume-controlled (VCV) or pressure-controlled ventilation (PCV) modes are most often used during OLV. This is a prospective observational analytical study of patients undergoing thoracic surgery with OLV. **Method:** 40 patients underwent thoracic surgery using one lung ventilation (OLV) from December 2023 to February 2024. All patients received lung protective ventilation (PLV) with a tidal volume of 6 ml/kgPBW during OLV with PEEP 5-7 cmH2O and were divided into two groups: one with a ventilator in volume-controlled mode (VCV) and the other with pressure-controlled mode (PCV). KL-6, CRP, and p/f ratio were measured before OLV, 2 hours after OLV, and 24 hours after the operation was completed. Respiratory variables during OLV were recorded. **Results:** KL-6 and CRP levels in PCV and VCV groups were significantly different. There were significant differences in the values of P_{peak} ($p < 0.001$), PEEP ($p = 0.008$), C_{stat} ($p = 0.004$) and driving pressure ($p < 0.001$) in both groups. The correlation between changes in KL-6 and CRP levels and the P/F ratio were very weak and insignificant. Cytokines play an important role in the inflammatory response in the lungs. Several determining factors of blood flow are gravity, lung disease, surgery, and hypoxic pulmonary vasoconstriction. Duration of OLV may affect the pulmonary inflammatory response and is correlated with the duration of OLV. **Conclusion:** There is no association found between KL-6 and CRP in PCV and VCV mode during thoracotomy with OLV.

Key words: One lung ventilation, Ventilator, CRP, KL-6, Thoracotomy.

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INTRODUCTION

One-lung ventilation (OLV) is a technique used during lung resection surgery to facilitate optimal surgery.[1] Volume-controlled ventilation (VCV) or pressure-controlled ventilation (PCV) modes are most often used during OLV. VCV mode ensures a stable and precise ventilation volume, but produces higher peak pressure which can cause barotrauma and non-uniform gas distribution. On the other hand, PCV improves arterial oxygenation, but is associated with lung injury due to traction forces on the lungs and alveoli. The best approach to OLV remains controversial. When OLV is performed, there is a significant decrease in lung volume, decreased lung compliance in the lateral decubitus position, formation of an intrapulmonary shunt and ventilator induced lung injury (VILI) in the dependent lung.[2]

Acute lung injury (ALI) biomarkers can be used for diagnosis, risk stratification/prediction, therapeutic surveillance, and adjustment of targeted therapy. Krebs von de Lungen-6 (KL-6) produced by type II pneumocytes is increased in patients with acute respiratory distress syndrome (ARDS).[3] Elevated C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) occurs during inflammation.[4] CRP is used as an inflammation biomarker because it is more routinely used and cost-effective.[5]

Until now, there have been no studies examining the influence of ventilator mode during OLV on lung biomarkers. Therefore, the authors are interested in studying the effect of ventilator mode during OLV procedures on the CRP inflammatory response and KL-6 levels as biomarkers of lung damage during thoracic surgery at Dr Soetomo General Hospital.

METHODS

This research is a prospective, observational analytical study of patients undergoing thoracic surgery undergoing OLV procedures with outcomes in the form of lung injury markers, namely CRP and KL-6. The research was conducted in the thoracic surgery operating room at RSUD Dr. Soetomo, Surabaya after obtaining ethical clearance. The research was carried out until the minimum sample size was met. The total sample required plus a dropout value of 10% is 36 patients (18 samples per group).

Inclusion criteria were patients aged ≥18 years, physical status American Society of Anesthesiologists (PS ASA) I-III, undergoing OLV for at least 2 hours, obtaining family approval to participate and signing informed consent.

Patients were excluded if: (1) had immune system disorders, arrhythmias, congenital heart valve disease, congestive heart failure (CHF), unstable preoperative hemodynamics, renal insufficiency, pericardial effusion, left ventricular ejection fraction <40%, and obesity (BMI > 35 kg/m^2); (2) obstructive pulmonary disease; (3) pregnant; (4) history of previous lobectomy; (5) thyroid disorders; and (6) loss to follow up.

The dependent variables are levels of C-reactive Protein (CRP) and Krebs von den Lungen-6 (KL-6). The independent variables are airway pressure (P_{peak} and P_{plateu}), compliance, driving pressure, and OLV duration. Confounding variables were duration of surgery and comorbidities.

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Fentanyl 2 mcg/kg IV bolus, propofol/etomidate 1-2 mg/kg, relaxants with rocuronium 0.6 mg/kg or atracurium 0.5 mg/kg were used as anesthesia induction. Maintenance anesthesia with isoflurane gas 1.2 Vol% or sevoflurane 2.0 Vol% 3 lpm. The anesthesiologist will set the ventilator according to protocol with PCV mode in group A and VCV in group B with a target VT 6 ml/kg PBW, RR 12-20 times/minute PEEP 5-10 cmH2O, I:E 1:1.5- 2, FiO2 50-100% with target SpO2 > 95% and ETCO2 35-45 mmHg. Blood samples were taken 1 hour after DLT intubation (T0), 2 hours after OLV (T1), and 24 hours post-surgery (T2) of 3 ml each from the median cubital vein or cephalic vein for examination of BGA, CRP and KL- 6 of ABP catheters.

Data will be analyzed using the SPSS 24.0 program. Shapiro Wilkinson normality test was initially performed. If the data is normally distributed, the ANOVA comparative test will be used, whereas if not, Friedman test will determine the differences in CRP and KL-6 levels between the 3 point of times. Pearson test is used for correlation analysis if the data is normal or Spearman test if the data is not normally distributed.

RESULTS

The research was conducted in the thoracic surgery operating room at RSUD Dr. Soetomo Surabaya from December 2023 to March 2024 involving patients who underwent thoracotomy and VATS surgery with the OLV approach and met the inclusion and exclusion criteria. The number of patients enrolled in the study was 41, one dropped out due to clinical worsening and intraoperative desaturation and two dropped out due to extreme result of KL-6. There were total of 38 participants who completed the study.

Characteristics of participants

This study involved 38 patients, the number of male was 25 (65.8%) and 13 (34.2%) female with an mean age of 48 years. Twenty patients used PCV ventilator mode while the rest used VCV ventilator mode. The most common comorbidity was hypertension in both groups. There were no significant differences of demographic data between the groups. Detailed characteristics of participants are presented in Table 1.

Comparison of KL-6 and CRP levels before OLV, 2 hours after OLV, and 24 hours post-surgery in PCV and VCV

KL-6 and CRP levels in the PCV and VCV groups were significantly different at each measurement point and continued to increase from before OLV, 2 hours after OLV, and 24 hours after surgery (Table 2). In addition, there were significant differences in KL-6 and CRP levels between the measurement times of T0 and T1, T0 and T2, and T1 and T2 in both the PCV and VCV ventilator mode groups ($p < 0.001$).

Comparison of P/F ratio levels before OLV, 2 hours after OLV, and 24 hours post-surgery in PCV and VCV modes

The P/F ratio levels in the PCV and VCV groups decreased at 2 hours of OLV and increased at 24 hours after surgery. There were differences in P/F Ratio levels at each measurement point ($p<0.001$) (Table 3).

Comparison of the P/F ratio in PCV mode between T0 vs T1, between T0 vs T2, and between T1 vs T2 shows $p <0.001$, $p = 0.108$, and $p = 0.444$, respectively. These indicate significant difference between T0 and T1. In VCV mode, there are significant differences in P/F ratio levels at the three point of times.

Comparison of respiratory parameters during OLV in PCV and VCV ventilator modes

This study also assessed the values of $EtCO_2$, P_{peak}, PEEP, C_{stat}, FiO_2, and driving pressure as respiratory parameters intrasurgery. Statistical analysis using independent t-test and Mann-Whitney revealed significant differences in the values of P_{peak} ($p = <0.001$), PEEP ($p = 0.008$), C_{stat} ($p = 0.004$) and driving pressure ($p <0.001$) in the VCV and PCV mode groups. Meanwhile, there were no differences in other variables (Table 4). The mean of P_{peak} in the VCV group was higher the PCV group.

Table 1. Demographic of participants undergoing OLV.

Characteristics	PCV (N=19)	VCV (N=19)	P value
Gender (F/M)	5/14	8/11	0.305
Age (years)	58 (17 – 80)	51 (17 – 64)	0.121
Body weight (kg)	57.2 (±10.5)	52.1 (±11.5)	0.161
Height (m)	1.6 (1.5 – 1.7)	1.6 (1.5 – 1.7)	0.354
BMI (kg/m²)	22.2 (±3.9)	20.7 (±4.4)	0.258
Duration of surgery (minutes)	205.8 (±71.7)	184.2 (±63.9)	0.334
OLV duration (minutes)	163.7 (±63)	152.9 (±58.7)	0.588
Duration of anesthesia (minutes)	335 (115 – 420)	300 (130 – 435)	0.279
Comorbidities (%)			
Pleural Effusion	3 (15.8)	3 (15.8)	1,000
COPD	1 (5.3)	1 (5.3)	1,000
Pneumonia	2 (10.5)	1 (5.3)	0.547
TB	6 (31.6)	2 (10.5)	0.111
Hypertension	6 (31.6)	4 (21.1)	0.461
DM	2 (10.5)	3 (15.8)	0.631
Misc.	1 (5.3)	2 (10.5)	0.547
Diagnosis (%)			
Lung Tumor	6 (31.6)	5 (26.3)	0.721
BPF	5 (26.3)	3 (15.8)	0.426
Pulmonary TB	6 (31.6)	6 (31.6)	1,000
Pneumothorax	11 (57.9)	7 (36.8)	0.194
Hematothorax	3 (15.8)	5 (26.3)	0.426
Rib Fracture	2 (10.5)	4 (21.1)	0.374
Mediastinal Tumor	0	2 (10.5)	0.146
Empyema	2 (10.5)	2 (10.5)	1,000
Misc	3 (15.8)	4 (21.1)	0.676
PS ASA (II/III)	5/14	7/12	0.485
Surgical method (%)			
Thoracotomy	12 (63.2)	13 (68.4)	
VATS	4 (21.1)	3 (15.8)	0.913
VATS Thoracotomy	3 (15.8)	3 (15.8)	
Pain Management (Epidural/ SAP)			
Epidural	5 (26.3)	8 (42.1)	
SAP	13 (68.4)	11 (57.9)	0.395
ESP	1 (5.3)	0	
Side (Right/Left)	9/10	10/9	0.746
Post Op (Tube In/Extubation)	6/13	3/16	0.252
Amount of intraoperative bleeding (ml)	350 (25 – 1,500)	200 (50 – 1,500)	0.988
EBL bleeding (>30%/≤30%)	2/17	3/16	0.631

Table 2. Comparison of KL-6 and CRP levels with PCV and VCV modes at T0, T1 and T2.

Parameter	T0 median (min-max)	T1 median (min-max)	T2 median (min-max)	P-value
KL-6				
PCV	96.8 (55.6 – 274.6)	98.9 (58.3 – 313.7)	143.3 (68.3 – 410.6)	<0.001*
VCV	72.2 (35.3– 444.5)	81.7 (42.9 – 504.3)	89.4 (63.2 – 559.9)	<0.001*
CRP				
PCV	2 (0.1 – 18)	4,1(0,1 – 22,2)	7.1 (0.2 – 29.1)	<0.001*
VCV	2.8 (0.1 – 6.2)	4,1(0,2 – 27)	7.3 (0.8 – 35.6)	<0.001*

*significance value $p < 0.05$

Table 3. Comparison of P/F Ratio PCV and VCV modes at T0, T1 and T2.

Parameter	T0mean (±SD)	T1mean (±SD)	T2mean (±SD)	P-value
P/F Ratio				
PCV	378.4 (±79.6)	261.7 (±77.2)	307.2 (±122.5)	0.001*
VCV	414 (±79.1)	290.4 (±76.7)	347.1 (±106.9)	<0.001*

*significance value p < 0.05

Table 4. Comparison of intraoperative respiratory parameters.

Variable	VCV Mean (±SD) Median (min-max)	PCV Mean (±SD) Median (min-max)	P value
$EtCO_2$	34.4 (±2.3)	33.7 (±2.2)	0.292
P_{peak}	26.8 (±1.2)	24.8 (±1.1)	<0.001*
PEEP	5 (5 – 8)	5 (5 – 6)	0.008*
C_{stat}	15.5 (±2)	17.4 (±1.8)	0.004*
FiO_2	50 (50 – 70)	50 (50 – 80)	0.663
Driving pressure	21.1 (±0.8)	19.6 (±1)	<0.001*

*significance value p < 0.05

Table 5. The association between respiratory parameters and KL-6 levels, CRP, and P/F Ratio during OLV.

Respiration Parameters	KL-6 T1	CRP T1	P/F ratio T1
$EtCO_2$ (N)	0.551	0.040*	0.273
P_{peak} (N)	0.001*	0.987	0.092
PEEP	0.120	0.214	0.730
C_{stat} (N)	0.167	0.457	0.455
FiO_2	0.067	0.526	0.261
Driving pressure (N)	0.001*	0.760	0.109

*significance value < α 0.05

Table 6. Correlation between the duration of surgery, OLV, and anesthesia with changes in KL-6 levels, CRP, and P/F ratio in patients during OLV.

Variables	KL-6 (T0-T1)	KL-6 (T1-T2)	CRP (T0-T1)	CRP (T1-T2)	P/F ratio (T0-T1)	P/F ratio (T1-T2)
Duration of surgery	0.112	0.007*	0.662	0.882	0.584	0.835
Duration of OLV	0.106	0.024*	0.913	0.798	0.967	0.962
Duration of Anesthesia	0.111	<0.001*	0.510	0.753	0.756	0.852

*significance value p < 0.05

The association between respiratory parameters and KL-6, CRP, and P/F ratio during OLV

Statistical analysis showed an association between the P_{peak} and driving pressure and KL-6 levels in patients during OLV, with significance values of 0.001 and 0.001 (p<0.05) (Table 5).

Correlation of duration of surgery, OLV, and anesthesia with changes in KL-6, CRP, and P/F ratio levels

The Spearman test showed an association between the duration of surgery, OLV, and anesthesia with changes in KL-6 levels from 2 hours after OLV to 24 hours post-surgery with a p value <0.05 (Table 6).

Correlation of surgical methods with changes in KL-6 levels, CRP, and P/F ratio

The results of statistical analysis showed that there was a relationship between the surgical method and changes in KL-6 and CRP levels from 2 hours after OLV to 24 hours after surgery with a p value <0.05. Apart from that, there is a relationship between the surgical method and changes in CRP levels before OLV and 2 hours after OLV with a p value of 0.002.

Correlation of changes in KL-6 and CRP levels during OLV

The correlation between changes in KL-6 and CRP levels in patients before OLV and 2 hours after OLV had a correlation coefficient of 0.028 (very weak) and obtained a p value of 0.868, which means there was no relationship between changes in KL-6 levels and changes in CRP levels in patients before OLV, and 2 hours after OLV. Correlation test of changes in KL-6 levels with CRP in patients 2 hours after OLV and 24 hours after surgery also did not show a significant relationship. The correlation between changes in KL-6 levels and changes in CRP levels was 0.212 (very weak) and insignificant.

Correlation of changes in KL-6 levels and P/F ratio during OLV

The correlation between changes in KL-6 levels and the P/F Ratio in patients before OLV and 2 hours after OLV had a correlation coefficient of 0.028 (very weak) with a p value of 0.866, which means there is no significant relationship. Changes in KL-6 levels and P/F Ratio at 2 hours after OLV and 24 hours after surgery showed a p value = 0.398, so no significant relationship was found. In addition, the correlation coefficient has a very weak relationship (r = -0.141).

Correlation of changes in CRP levels and P/F ratio during OLV

The correlation between changes in CRP levels and the P/F Ratio before OLV and 2 hours after OLV has a value of p=0.450. Changes in CRP levels with P/F Ratio at 2 hours after OLV and 24 hours after surgery obtained a value of p=0.693. Both mean there is no meaningful relationship. The correlation between changes in CRP levels and P/F Ratio levels at 2 hours after OLV and 24 hours after surgery has a value of -0.066 (very weak) and is not significant.

DISCUSSION

This study involved 38 patients who underwent thoracic surgery using the one lung ventilation method. In general, the proportion of male subjects was greater (65.8%). An observational study in France showed similar results, where the number of patients undergoing surgery with male OLV was greater (86.7%) than female. The most frequently used post-operative pain management is peripheral nerve block using the serratus anterior plane block method. This is important because pain is one of the factors that can cause an increase in inflammatory mediators.[6]

It was found that KL-6 and CRP levels in the PCV and VCV groups was significantly different at each measurement point and continued to increase from before OLV, 2 hours after OLV, and 24 hours after surgery. It was found that KL-6 levels were lower in the VCV group. Serum KL-6 levels have been shown to correlate with the alveolar-capillary permeability index, suggesting a link between serum KL-6 and barrier dysfunction of the alveolar epithelium.[7] Nathani et al. In his research, KL-6 levels in plasma reflected the severity of lung injury and the highest KL-6 levels were found in the group where mortality occurred later in life.[8]

Several factors may trigger ALI during OLV at thoracotomy. During OLV, the operated lung experiences atelectasis and hypoperfusion may occurs due to hypoxic vasoconstriction. Lung re-expansion and tissue reperfusion also lead to ischemia-reperfusion injury, which may explain the inflammatory mechanism during OLV. In addition, the remaining post-resection tissue has also been manipulated during surgery, which may also contribute to the inflammatory response.[9]

CRP levels in the PCV group were lower than those in the VCV group. In this study, differences were found in CRP levels in patients with PCV and VCV ventilator modes performed before OLV (T0), 2 hours after OLV (T1), and 24 hours after surgery. C-reactive protein (CRP) is a response protein in the acute phase type 1 that is synthesized in the liver and regulated by proinflammatory cytokines such as IL-6, IL-1, and TNF-α. An increment of CRP level is used as a prognostic factor in various medical conditions. The use of mechanical ventilation, especially with large tidal volume can cause VILI where cytokines play an important role in the inflammatory response in the lungs. Cytokines then enter the peripheral blood to recruit inflammatory cells back to the lungs and aggravate pulmonary damage. Therefore, serum CRP concentrations are determined by the rate of synthesis, reflecting the acute inflammatory response.[10,11]

In this study, changes in the P/F ratio were similar as both decrease at the time of examination 2 hours after OLV, and an increase again after 24 hours after surgery. Several things determine blood flow to the operated lung, such as gravity, underlying lung disease, surgical intervention including pulmonary artery clamping, and hypoxic pulmonary vasoconstriction.[12] P/F ratio levels were also lower in the PCV group compared to VCV at three measurement points. This could be caused by differences in the baseline P/F ratio and older age in the PCV group. Lin et al found that almost all elderly who were on mechanical ventilation will develop mild, moderate or severe atelectasis and shunts.

We found that use of PCV mode did not improve oxygenation when compared with VCV mode. Similar results were obtained by Unzueta et al that the use of PCV during OLV did not result in increased oxygenation compared with VCV for patients with well-functioning preoperative lung conditions. However, in the PCV group P_{peak} was lower compared to the VCV group, in line with this study.[13]

There were significant differences in P_{peak} ($p = <0.001$), PEEP ($p = 0.008$), C_{stat} ($p = 0.004$) and driving pressure ($p <0.001$) values in both groups. VCV mode produces stable MV, but with this mode there is a higher airway pressure which can cause barotrauma and volutrauma which can cause uneven gas distribution in the lungs. In contrast, the PCV mode produces lower airway pressure with a decelerated flow pattern, but this can cause lung trauma due to tractive forces on the alveoli. Unzueta et al also obtained similar results where P_{peak} in the PCV group (24.43 ± 3.42) was found to be lower than in the VCV group (34.16 ± 5.21) during OLV.[13]

In patients receiving positive pressure ventilation, for example in patients on mechanical ventilation, high P_{peak} or P_{lateau} can increase transpulmonary pressure which can then have adverse effects.[14] Increased airway pressure caused by mechanical ventilation is a risk factor for VILI. However, in this study, KL-6 levels were found to be higher in the PCV group when compared with the VCV group. This could be due to the difference in baseline KL-6 from patients with PCV mode which is indeed higher compared to patients with VCV mode.[15] There was no correlation between all respiratory parameters with CRP levels and P/F ratio during OLV. This could be due to the application of LPS during OLV.

This study shows the relationship between duration of surgery, duration of OLV, and duration of anesthesia with changes in KL-6 from 2 hours after OLV to 24 hours after surgery. The duration of OLV is one of the main factors determining the pulmonary inflammatory response and the pulmonary inflammatory response is correlated with the duration of OLV. De Conna in his research found that there was an increase in inflammatory cytokines which was directly proportional to the duration of OLV.[10] Fiorelli et al showed that OLV in a short period of time (64.44±21.68 minutes) did not affect the local inflammatory cytokine response.[16] Lai et al showed significant differences in PaO_2 with duration of OLV.[17] Similarly, Sugasawa et al found that OLV can trigger an inflammatory response during lung resection and the duration of OLV was 140.6±12.6 minutes.[18]

The inflammatory response is affected by the duration of surgery, duration of OLV, mechanical ventilation, and tissue trauma due to surgery. Misthos et al found that an increase in oxidative stress was related to the duration of OLV, where the longer the OLV, the greater the oxidative stress ($p < 0.001$). The results of univariate analysis showed that the incidence of acute respiratory failure, arrhythmias, and pulmonary hypertension was higher in the group with OLV duration ≥120 minutes.[19]

Patients who undergo thoracotomy are at greater risk for complications that can be caused by existing disease processes, the effects of surgery, loss of lung parenchymal function in patients with pulmonary resection, and the effects of mechanical ventilation, especially during OLV.[20] The use of less invasive surgical techniques and more advanced anesthetic management is recommended to improve outcomes as VATS has been shown to require less operative time, minimal bleeding on surgery, shorter duration of postoperative chest tube insertion, and shorter duration for a postoperative stay.[15,21] Auginalgade et al found that respiratory complications occurred more frequently in the thoracotomy group compared to the VATS group.[22]

Limitations of this research are that the sample is not homogeneous. Preoperative spirometry examination is required. Second, the study population was from a single medical center, so results may not be generalizable to the general population. Further research is needed by measuring biomarkers of lung damage using brochoalveolar lavage fluid samples in both dependent and non-dependent lungs, larger and more homogeneous sample numbers, and assessing post-OLV lung complications.

CONCLUSION

There is no association found between KL-6 and CRP in PCV and VCV mode in thoracotomy with OLV. However, there are differences between KL-6 levels in PCV and VCV mode, as well as between CRP in PCV mode and VCV in thoracotomy and OLV.

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DISCLOSURE

The authors have stated their absence of any conflicts of interest regarding this study.

AUTHORS' CONTRIBUTIONS

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

ETHICAL CONSIDERATION

Ethical committee approval for this study was obtain from Dr Soetomo General Hospital, Airlangga University; the approval certificate number is 0849/KEPK/XII/2023.

DATA AVAILABILITY

The article contains all the necessary data to support the results; no supplementary source data is needed.

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