Title
Effects of hypercarbia on arterial oxygenation during one-lung ventilation: prospective randomized crossover study.

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Running title
Hypercarbia during One Lung Ventilation

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Conflict of interest

The authors declare no competing interests

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Effects of hypercarbia on arterial oxygenation during one-lung ventilation: prospective randomized crossover study

Running title: Hypercarbia during One-Lung Ventilation
Abstract

Background: The present study was designed to evaluate the effects of hypercarbia on arterial oxygenation during one-lung ventilation (OLV).

Methods: Fifty adult patients undergoing elective video-assisted thoracoscopic lobectomy or pneumonectomy were enrolled. Group 1 patients (n = 25) were first maintained in normocarbia (PaCO$_2$: 38 - 42 mmHg) for 30 min and then in hypercarbia (45 - 50 mmHg). In group 2 patients (n = 25), PaCO$_2$ was maintained in the reverse order. Arterial oxygen partial pressure (PaO$_2$), respiratory variables, hemodynamic variables, and hemoglobin concentration were compared during normocarbia and hypercarbia. Arterial O$_2$ content and O$_2$ delivery were calculated.

Results: PaO$_2$ values during normocarbia and hypercarbia were 66.5 ± 10.6 mmHg and 79.7 ± 17.3 mmHg, respectively, (mean difference: 13.2 mmHg, 95% CI for difference of means: 17.0 to 9.3, P < 0.001). SaO$_2$ values during normocarbia and hypercarbia were 92.5 ± 4.8% and 94.3 ± 3.1% (P = 0.009), respectively. Static compliance of the lung (33.0 ± 5.4 vs. 30.4 ± 5.3 mL/cmH$_2$O, P < 0.001), arterial O$_2$ content (15.4 ± 1.4 vs. 14.9 ± 1.5 mL/dL, P < 0.001) and O$_2$ delivery (69.9 ± 18.4 vs. 65.1 ± 18.1 mL/min, P <0.001) were significantly higher during hypercarbia than during normocarbia.

Conclusions: Hypercarbia increases PaO$_2$ and O$_2$ carrying capacity and improves pulmonary mechanics during OLV, suggesting that it may be helpful to manage oxygenation during OLV. Therefore, permissive hypercarbia may be a simple and valuable modality to manage arterial oxygenation during OLV.

Keywords: Arterial oxygen partial pressure; Carbon dioxide; Hypercarbia; One-lung ventilation; Shunt; Thoracic surgery.
Introduction
Presently, many thoracic surgeries require one-lung ventilation (OLV) to improve the operation field and expedite the operation. During OLV, maintenance of adequate arterial oxygenation is a major concern to anesthesiologists. In previous studies, 4–27% of patients undergoing OLV develop arterial hypoxemia.\(^1\)\(^-\)\(^3\) Because a collapsed lung is not ventilated but perfused, a transpulmonary shunt is inevitably developed, which leads to impairment of oxygenation. In addition, atelectatic and hypoventilated areas are increased in the dependent ventilated lung by the positional effects during thoracic surgery with OLV in the lateral position, which contributes to ventilation/perfusion mismatch and decreases arterial oxygen partial pressure (PaO\(_2\)).

Hypoxic pulmonary vasoconstriction (HPV) is a physiologic mechanism that decreases blood flow to hypoxic or atelectatic lung regions by arteriolar vasoconstriction via a pathway involving nitric oxide and/or cyclooxygenase synthesis inhibition.\(^4\) HPV diverts pulmonary blood flow from poorer ventilated areas to better areas of the lung, thus reducing the shunt fraction and improving oxygenation.\(^5\)\(^,\)\(^6\) Although HPV reduces shunt flow, 15 - 40% of pulmonary blood shunts to the left heart during OLV.\(^7\) Recommendations to prevent arterial hypoxemia during OLV include the use of high inspired fraction of oxygen (F\(_{\text{I}}\)O\(_2\)), application of positive end-expiratory pressure (PEEP) to the dependent lung, and continuous positive airway pressure (CPAP) to the non-dependent lung.\(^8\) However, these techniques are inadequate for maintaining adequate oxygenation in some patients undergoing OLV.

In clinical practice, many of patients have hypercarbia due to decreased minute ventilation and increased dead-space ventilation during OLV compared to two-lung ventilation (TLV). Carbon dioxide (CO\(_2\)) is a potent vasodilator in cerebral and systemic circulation.\(^9\)\(^,\)\(^10\) However, the effect of CO\(_2\) on pulmonary circulation is unclear. In previous studies\(^10\)\(^-\)\(^14\), the effects of CO\(_2\) on the pulmonary vessels were various by the experiment species and pulmonary vascular tone. Most
previous studies were conducted on the ventilated lungs, but studies on the one-lung ventilation subjects are rare. If CO₂ dilates the pulmonary artery in the ventilated lung or constricts the pulmonary artery in the non-ventilated lung, then hypercarbia may increase arterial oxygenation during OLV. If CO₂ has the opposite effects, then hypercarbia should be avoided.

We hypothesized that hypercarbia increase arterial oxygenation compared with normocarbia during OLV. The primary purpose of this prospective, randomized crossover study was to evaluate the effects of hypercarbia on arterial oxygenation during OLV.
Materials and Methods

This prospective, randomized crossover study was approved by the Institutional Review Board of Chonbuk National University Hospital and registered with the WHO International Clinical Trials Registry Platform (KCT0003185). Written informed consent was obtained from all participants. Fifty adult patients who were assigned ASA physical status I or II, and who underwent elective video-assisted thoracoscopic lobectomy or pneumonectomy due to lung cancer were enrolled in the study. Patients who presented cardiac arrhythmia, heart failure, chronic obstructive pulmonary disease, restrictive pulmonary disease or increased intracerebral pressure were excluded. Subjects were randomly assigned using a computer-generated block randomization scheme to one of two groups (1:1 allocation ratio). Arterial oxygenation can be greatly affected by surgical process such as ligation of the pulmonary vessels in the collapsed surgical lung. Therefore, we divided the patients into two groups by the order of intervention although it is a crossover comparison. After initiation of OLV, group 1 patients were first maintained at normal arterial CO\textsubscript{2} partial pressure (normocarbia, PaCO\textsubscript{2}: 38 - 42 mmHg) for 30 min (OLV-1) and then in high PaCO\textsubscript{2} (hypercarbia, 45 - 50 mmHg) for 30 min (OLV-2). In group 2 patients, PaCO\textsubscript{2} was maintained in the reverse order (OLV-1, hypercarbia; and OLV-2, normocarbia).

The anesthetic regimen was standardized for all patients. After placement of the electrocardiogram, pulse oximetry, non-invasive blood pressure, bispectral index (BIS) and peripheral nerve stimulator, anesthesia was induced with 1.0 - 1.5 mg kg\textsuperscript{-1} propofol, 4 - 6 ng ml\textsuperscript{-1} effect-site concentration of remifentanil, and 1.0 mg kg\textsuperscript{-1} rocuronium. Remifentanil was administered using a Minto model effect-site target-controlled infusion pump (Orchestra® Base Primea, Fresenius Vial, Brézins, France). Patients were manually ventilated using a face mask with sevoflurane (4.0 vol% in 50% oxygen) until a train-of-four count of 0 in the peripheral nerve stimulator was obtained. Female and male patients were intubated with a 35 or 37 Fr. and 37 or 39
Fr. left-sided double-lumen tube (Shiley™ Endobronchial tube left, Covidien, MA, USA), respectively. The double-lumen tube was positioned using a fiberoptic bronchoscope. After induction of anesthesia, a 20-G arterial catheter was inserted into the brachial artery in the non-dominant hand. The brachial artery catheter was connected to the FloTrac™ transducer (Edwards Lifesciences, Irvine, CA, USA) coupled to both an anesthesia workstation (Primus Infinity® Empowered, Dräger, Lübeck, Germany) and EV1000™ (software version 1.5, Edwards Lifesciences) for hemodynamic measurements including invasive blood pressure (IBP), cardiac index (CI), stroke volume variation (SVV), and systemic vascular resistance index (SVRI). Right subclavian vein was catheterized under an ultrasono-guide for intravenous fluid line, central venous blood gas analysis and central venous pressure (CVP) measurement. Pressure transducers were zeroed at the cardiac level to atmospheric pressure.

Lungs were mechanically ventilated with 0.5 of F\textsubscript{1}O\textsubscript{2} using a tidal volume (TV) of 6 - 8 ml kg\textsuperscript{-1} predicted body weight, an inspiratory to expiratory ratio of 1:2, an inspiratory pause of 25% of total inspiration time, and 5 cmH\textsubscript{2}O of PEEP. Ventilatory rate was adjusted to maintain normocapnia. Anesthesia was maintained with sevoflurane and remifentanil. Fresh gas flow was fixed 3 L/min. End-expiratory sevoflurane concentration was fixed to 1.0 vol%. Arterial blood pressure was kept within 20% of preanesthetic values by adjustment of remifentanil concentration. Initially, the end-tidal CO\textsubscript{2} (E\textsubscript{T}CO\textsubscript{2}) and BIS value were maintained at 35 to 38 mmHg and 40 to 60, respectively. If the patient showed > 60 BIS value, the patient received midazolam and excluded from the data analysis.

After changing to the lateral position, the position of the double-lumen tube was reconfirmed using a fiberoptic bronchoscope. An arterial and central venous blood sample was obtained in the lateral position with two-lung ventilation after an alveolar recruit maneuver. After arterial blood gas analysis, the difference between PaCO\textsubscript{2} and E\textsubscript{T}CO\textsubscript{2} was evaluated. During OLV,
TV was not changed. The F\textsubscript{1}O\textsubscript{2} was initially set at 0.5 and adjusted to maintain arterial O\textsubscript{2} saturation above 90%. The F\textsubscript{1}O\textsubscript{2} was not changed during the study period. If the patients showed pulse oximetric oxygen saturation (S\textsubscript{p}O\textsubscript{2}) lower than 90% in F\textsubscript{1}O\textsubscript{2} 0.5, the F\textsubscript{1}O\textsubscript{2} was increased the patients were excluded from the data analysis. The ventilatory rate was adjusted to maintain the preset target PaCO\textsubscript{2}. In all patients, normocarbia and hypercarbia periods were stable for 30 min because HPV reaches a plateau by 20 to 30 min.\textsuperscript{15,16}

The primary endpoint of the study was PaO\textsubscript{2} in normocarbia and hypercarbia during OLV. The PaO\textsubscript{2} was recorded at TLV, OLV-1 and OLV-2. In group 1 patients, OLV-1 was normocarbia and OLV-2 was 30 min after hypercarbia. OLV-1 and OLV-2 were hypercarbia and normocarbia, respectively, in Group 2. At the time of measurement, the following respiratory and hemodynamic variables were recorded: expiratory TV, ventilatory rate, peak inspiratory pressure (P\textsubscript{IP}), plateau pressure (P\textsubscript{PL}), IBP, CVP, CI, SVV, and SVRI. The dynamic (C\textsubscript{dy}) and static compliances (C\textsubscript{st}) were calculated using the following equations: C\textsubscript{dy} = TV/ P\textsubscript{IP} - PEEP and C\textsubscript{st} = TV/ P\textsubscript{PL} - PEEP. Arterial blood gas, hemoglobin (Hg) concentration and lactate concentration were also recorded. Central venous blood gas analysis was performed to measure oxygen partial pressure (PcvO\textsubscript{2}) and saturation (ScvO\textsubscript{2}) of central venous blood. Arterial O\textsubscript{2} content (CaO\textsubscript{2}) was calculated by the following equation: CaO\textsubscript{2} = 1.39 x Hg concentration x SaO\textsubscript{2} + 0.0031 x PaO\textsubscript{2}. Oxygen delivery (DO\textsubscript{2}) was calculated by the following equation: DO\textsubscript{2} = CaO\textsubscript{2} x CO.
**Statistical analysis**

Sample size was predetermined by paired t-test sample size test using SigmaPlot 13.0 (Systat Software Inc. San Jose, USA) based on the assumption that a pilot study of 10 patients for PaO$_2$ difference between hypercarbia and normocarbia during OLV, which was the primary endpoint, showed an average of 10 mmHg and a standard deviation of 18 mmHg. For PaO$_2$ difference, a value of $\geq 10$ mmHg was considered to be clinically significantly different. It was determined that 34 patients were required to obtain a difference in mean PaO$_2$ of 10 mmHg for an expected standard deviation of 20 mmHg with a significance level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). To allow for attrition, the sample size was increased to 50 patients.

The PaO$_2$ measured for OLV-1 and OLV-2 were analyzed via linear mixed-effects (LME) modeling using SPSS 23.0 (IBM Corp, Armonk, USA). The linear mixed model included the variables id (random effect), presence of hypercarbia (OLV-1 and OLV-2), the sequence of ventilation (OLV-1 first versus OLV-2 first) , and interaction between presence of hypercarbia and the sequence of ventilation. LME modeling produced restricted maximum likelihood estimation fits. LME modeling was used to assess whether there was a differential carryover effect of the first given treatment. Patient and clinical characteristics were analyzed with unpaired t-tests or Chi-square tests. Blood gas analysis, hemodynamic variables, and respiratory variables were compared with unpaired t-tests between groups 1 and 2. Data are presented as the mean ± SD. The $\alpha$ value adjustment with Bonferroni correction was done to compensate for multiple comparisons within primary outcomes. The $\alpha$ value was adjusted to 0.016 instead of 0.05. The P values were compared with this adjusted $\alpha$ value in interpreting primary outcome measures. Otherwise, P values $< 0.05$ were deemed to indicate statistical significance.
Results

Of the 50 allocated surgical patients, 5 patients whose pulmonary artery was ligated before final measurement and 2 patients who showed arterial oxygen saturation less than 90% in spite of FiO₂ 1.0 thus requiring CPAP to the non-dependent lung and 3 patients who received midazolam were excluded from the analysis (Fig. 1). During OLV, 40, 4, and 6 patients were maintained with FiO₂ 0.5, 0.8, and 1.0, respectively. No patient required transfusion during the operation. The demographic and preoperative clinical characteristics of the patients are shown in Table 1. The differential carryover effect of a preceding ventilation technique over a following ventilation technique and interaction between presence of hypercarbia and the sequence of ventilation were statistically insignificant (P = 0.771 and P = 0.713).

The PaCO₂ values during normocarbia and hypercarbia were 38.8 ± 2.6 mmHg (mean ± SD) and 48.2 ± 2.4 mmHg, respectively. In both groups, PaO₂ was significantly decreased to convert from TLV to OLV, but PaO₂ was higher during hypercarbia than normocarbia. PaO₂ values during normocarbia and hypercarbia were 66.5 ± 10.6 mmHg and 79.7 ± 17.3 mmHg, respectively, (mean difference: 13.2 mmHg, 95% CI for difference of means: 17.0 to 9.3, P < 0.001). Arterial O₂ saturation (SaO₂) values during normocarbia and hypercarbia were 92.5 ± 4.8% and 94.3 ± 3.1% (P = 0.009), respectively. For individual patients, PaO₂ was increased by changing the PaCO₂ from normocarbia to hypercarbia in 37 of 40 patients (93%) (Fig. 2). During normocarbia, pH was 7.42 ± 0.04 but, 7.35 ± 0.04 during hypercarbia (P < 0.001).

Although fixed TV was applied, P_\text{IP} and P_\text{PL} were significantly lower during hypercarbia than normocarbia in both groups. Based on these results, C_\text{dyn} and C_\text{stat} were higher during hypercarbia than normocarbia (Table 2). The hemodynamic variables, including IBP, HR, CI, CVP, SVV and SVRI, as well as the hemoglobin concentration and BIS during normocarbia were comparable to hypercarbia in both groups. However, CaO₂ and DO₂ were significantly higher
during hypercarbia than during normocarbia (Table 3). PcvO$_2$, ScvO$_2$, and lactate concentration were significantly different between normocarbia and hypercarbia in both groups (Table 4).
Discussion

Although OLV provides optimum surgical conditions during thoracic surgery, it is associated with impairment in gas exchange. In addition to arterial hypoxemia, hypercarbia is commonly developed during OLV. Because atelectasis may readily occur in the dependent lung, application of PEEP are necessary to prevent atelectasis during OLV. Increased lung volume and PEEP elevate airway pressure. Increased airway pressure may impede perfusion of the dependent lung, leading to dead-space ventilation. Increased dead-space ventilation may cause hypoventilation and hypercarbia. Additionally, anesthesiologists are apt to reduce TV to prevent increased \( P_{IP} \) during OLV. For these reasons, hypercarbia is common in arterial blood gas analysis during OLV in clinical practice. In the present study, moderate hypercarbia increased \( PaO_2 \), \( SaO_2 \), \( CaO_2 \), \( DO_2 \), \( PcvO_2 \), \( ScvO_2 \), \( C_{dyn} \), and \( C_{stat} \) but decreased airway pressure and lactate concentration. These results were considered as positive effects on gas exchange during OLV.

The main cause of hypoxemia during OLV is the intrapulmonary shunt through the non-dependent, non-ventilated lung. Alveolar collapse in the non-dependent lung activates HPV, leading to an increase in resistance to flow in the dependent pulmonary artery, thus diverting more perfusion to the ventilated, dependent lung. In the present study, increased \( PaO_2 \) reflected as decreased intrapulmonary shunt during hypercarbia. Although the mechanism was not clarified, hypercarbia may increase pulmonary vascular resistance in the non-dependent lung or decrease pulmonary vascular resistance in the dependent, ventilated lung. A pulmonary vasoconstrictor almitrine enhances HPV and prevents the OLV-induced decrease in \( PaO_2 \). Inhaled nitric oxide has selective pulmonary vasorelaxation in the dependent, ventilated lung during OLV. Therefore, both almitrine and nitric oxide increase arterial oxygenation during OLV. Chuang et al. reported that inhaled CO\(_2\) has vasodilatory effects and that it reverses pulmonary hypertension induced by hypoxia in isolated perfused rat lungs. Previous studies have indicated that CO\(_2\) is a mild...
vasoconstrictor during basal tone condition but that it is a potent vasodilator at high pulmonary vascular resistance.\textsuperscript{14, 21-24} Unfortunately, the present results did not provide a mechanism because pulmonary vascular resistance and pulmonary blood flow were not measured in both lungs.

In the present study, the pH value was decreased by 0.06 – 0.08 during hypercarbia compared to normocarbia. A low pH shifts the oxyhemoglobin dissociation curve to the right by Bohr effects. As the curve shifts to the right, the SaO\textsubscript{2} for a given PaO\textsubscript{2} decreases, i.e. decreased hemoglobin affinity for O\textsubscript{2}.\textsuperscript{25} As the pH decreases from 7.40 to 7.35, similar to the decrease in the present study, hemoglobin releases O\textsubscript{2} more readily to tissues although oxygen uptake is reduced from the alveoli. Respiratory acidosis can potentiate HPV.\textsuperscript{26} Although the increase of PaO\textsubscript{2} was not excluded by the effects of acidosis in our results, hypercarbia provide positive effects to management of arterial hypoxemia during OLV in conjunction with increased CaO\textsubscript{2} and DO\textsubscript{2}. Accordingly, blood lactate concentration was lower during hypercarbia than normocarbia in both groups although the values were considered within normal ranges.

In the present study, P\textsubscript{IP} and P\textsubscript{PL} were significantly lower during hypercarbia than normocarbia in both groups although TV was not changed. Based on these results, C\textsubscript{dyn} and C\textsubscript{stat} were higher during hypercarbia than normocarbia. These results may reflect that increased CO\textsubscript{2} relaxes bronchiole and lung parenchyma. CO\textsubscript{2}-dependent regulation of lung compliance and ventilation-perfusion matching have been explained by pH- and CO\textsubscript{2}-dependent changes. Previous studies have reported that CO\textsubscript{2} relaxes lung parenchyma and increases lung compliance.\textsuperscript{27, 28} These effects of hypercarbia provide positive effects on ventilation/perfusion matching and management of arterial hypoxemia during OLV. However, the increased lung compliance during hypercarbia may be influenced by respiratory rate change. The results require further studies to clarify the mechanism.

The key points of lung protective mechanical ventilation strategies of the acute respiratory
distress syndrome (ARDS) are low TV and increased PEEP. The unintended consequences of the protective ventilation are hypercapnia and hypercapnic acidosis due to reduction in minute ventilation and a worsening of ventilation/perfusion mismatch. Previously, acidosis has been permitted as an adverse side effect of protective ventilation. However, several studies have shown the ability of CO\textsubscript{2} to protect against lung injury and repair independently of low TV\textsuperscript{29-33}. The concept has been changing from permissive hypercapnia to therapeutic hypercapnia in ARDS. OLV is associated with high rate of postoperative pulmonary complications, and OLV is currently recognized as a risk factor for acute lung injury\textsuperscript{34,35}. Although the pathophysiologic mechanism of acute lung injury after OLV is different for the ventilated and non-ventilated lung, hypercarbia may be helpful to prevent and/or repair acute lung injury after OLV.

There are two limitations to the current study. First, the results may be affected by surgical process. To exclude this effect, patients were divided into two groups in a different order although the study was designed for crossover comparison. Moreover, the study was discontinued if the pulmonary artery was ligated before the final measurement. Nevertheless, the results could be affected by operation. Therefore, it would be better if the study was performed before operation. Second, the present results did not provide a mechanism that hypercarbia increased PaO\textsubscript{2} during OLV because the pulmonary vascular resistance and pulmonary blood flow were not measured in both lungs as mentioned above. Further studies are needed to confirm the mechanism of hypercarbia.

In conclusion, hypercarbia increases PaO\textsubscript{2} and O\textsubscript{2} carrying capacity and improves pulmonary mechanics without significant hemodynamic changes during OLV. Thus, it may be helpful to manage oxygenation during OLV. Therefore, permissive hypercarbia may be a simple and valuable modality to manage arterial oxygenation during OLV.
References


Table 1. Demographic Data and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.0 ± 8.0</td>
<td>62.7 ± 7.8</td>
<td>0.195</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>7/13</td>
<td>7/13</td>
<td>0.740</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.1 ± 6.6</td>
<td>162.5 ± 8.5</td>
<td>0.578</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 ± 9.2</td>
<td>66.4 ± 11.9</td>
<td>0.145</td>
</tr>
<tr>
<td>ASA PS (1/2)</td>
<td>3/17</td>
<td>3/17</td>
<td>0.658</td>
</tr>
<tr>
<td>Operation site (Left/Right)</td>
<td>5/15</td>
<td>7/13</td>
<td>0.730</td>
</tr>
<tr>
<td>Preoperative lung function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.8</td>
<td>0.911</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>2.5 ± 0.5</td>
<td>2.5 ± 0.6</td>
<td>0.823</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>76.2 ± 5.9</td>
<td>75.8 ± 8.1</td>
<td>0.856</td>
</tr>
</tbody>
</table>

(PaCO₂: 38 - 42 mmHg) after then maintained hypercarbia (PaCO₂: 45 - 50 mmHg). In group 2 patients, PaCO₂ were maintained in a reverse order. ASA PS: American society of anesthesiologists physical status, FVC: functional vital capacity, FEV1: forced expiratory volume for 1 sec.
**Table 2. Respiratory Variables during One-Lung Ventilation**

<table>
<thead>
<tr>
<th></th>
<th>Normocarbia</th>
<th>Hypercarbia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (mL)</td>
<td>413.0 ± 50.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory rate (bpm)</td>
<td>15.3 ± 2.5</td>
<td>9.4 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cmH₂O)</td>
<td>24.8 ± 3.7</td>
<td>21.5 ± 2.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plateau pressure (cmH₂O)</td>
<td>18.9 ± 2.3</td>
<td>17.7 ± 1.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dynamic compliance (mL/cmH₂O)</td>
<td>21.3 ± 3.2</td>
<td>25.3 ± 3.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Static compliance (mL/cmH₂O)</td>
<td>30.4 ± 5.3</td>
<td>33.0 ± 5.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Lung Ventilation
### Table 3. Bispectral index, Hemoglobin Concentration, and Hemodynamic Variables during One-Lung Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Normocarbia</th>
<th>Hypercarbia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIS</strong></td>
<td>51.5 ± 8.7</td>
<td>52.4 ± 7.7</td>
<td>0.382</td>
</tr>
<tr>
<td>Hemoglobin conc. (g/dL)</td>
<td>11.4 ± 1.1</td>
<td>11.5 ± 1.1</td>
<td>0.179</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>79.6 ± 11.5</td>
<td>79.7 ± 11.3</td>
<td>0.899</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>68.2 ± 12.0</td>
<td>68.7 ± 11.5</td>
<td>0.575</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.6 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td>0.170</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>8.6 ± 3.6</td>
<td>8.8 ± 3.9</td>
<td>0.183</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>7.0 ± 2.9</td>
<td>7.3 ± 2.9</td>
<td>0.252</td>
</tr>
<tr>
<td>SVRI (dyne·sec·cm²/m²)</td>
<td>2150.5 ± 552.3</td>
<td>2120.2 ± 606.4</td>
<td>0.554</td>
</tr>
<tr>
<td>CaO₂ (mL/dL)</td>
<td>14.9 ± 1.5</td>
<td>15.4 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DO₂ (mL/min)</td>
<td>65.1 ± 18.1</td>
<td>69.9 ± 18.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

heart rate, CI: cardiac index, CVP: central venous pressure, SVV: stroke volume variation, SVRI: systemic vascular resistance index, CaO₂: arterial oxygen content, DO₂: oxygen delivery.
**Table 4.** Oxygen Partial Pressure (PcvO$_2$) and Saturation (ScvO$_2$) of Central Venous Blood and Lactate Concentration

<table>
<thead>
<tr>
<th></th>
<th>Normocarbia</th>
<th>Hypercarbia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PcvO$_2$ (mmHg)</td>
<td>38.8 ± 6.3</td>
<td>44.3 ± 4.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ScvO$_2$ (%)</td>
<td>70.1 ± 7.4</td>
<td>74.9 ± 5.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lactate concentration (mmol/L)</td>
<td>1.1 ± 0.4</td>
<td>1.0 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Fig. 1. CONSORT flow diagram. Group 1 patients were maintained firstly normocarbia (PaCO₂: 38 - 42 mmHg) after then maintained hypercarbia (PaCO₂: 45 - 50 mmHg). In group 2 patients, PaCO₂ were maintained in a reverse order. CPAP: continuous positive airway pressure.
Fig. 2. Arterial O$_2$ partial pressure was increased by changing the arterial CO$_2$ partial pressure (PaCO$_2$) from normocarbia to hypercarbia in 37 of 40 individual patients (93%). Group 1 patients were maintained firstly normocarbia (PaCO$_2$: 38 - 42 mmHg) after then maintained hypercarbia (PaCO$_2$: 45 - 50 mmHg). In group 2 patients, PaCO$_2$ were maintained in a reverse order.