Original Article

# Continuous positive airway pressure combined with small-tidal-volume ventilation on arterial oxygenation and pulmonary shunt during one-lung ventilation in patients undergoing video-assisted thoracoscopic lobectomy: A randomized, controlled study

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## Abstract:

**BACKGROUND:** One-lung ventilation (OLV) is frequently applied during video-assisted thoracoscopic surgery (VATS) airway management to collapse and isolate the nondependent lung (NL). OLV can give rise to hypoxemia as a result of the pulmonary shunting produced. Our study aimed to assess the influence of continuous positive airway pressure (CPAP) combined with small-tidal-volume ventilation on improving arterial oxygenation and decreasing pulmonary shunt rate ($Q_S/Q_T$) without compromising surgical field exposure during OLV.

**METHODS:** Forty-eight patients undergoing scheduled VATS lobectomy were enrolled in this research and allocated into three groups at random: C group (conventional ventilation, no NL ventilation intervention was performed), LP group (NL was ventilated with lower CPAP [2 $cmH_2O$] and a 40–60 mL tidal volume [TV]), and HP group (NL was ventilated with higher CPAP [5 $cmH_2O$] and a 60–80 mL TV). Record the blood gas analysis data and calculate the $Q_S/Q_T$ at the following time: at the beginning of the OLV (T0), 30 min after OLV (T1), and 60 min after OLV (T2). Surgeons blinded to ventilation techniques were invited to evaluate the surgical fields.

**RESULTS:** The demography data of the three groups were consistent with the surgical data. At T1, $PaO_2$ in the HP group was substantially higher compared to the C group ($P < 0.05$), while there was no significant difference in the LP group ($P > 0.05$). At T1-T2, $PaCO_2$ in the LP and HP groups was significantly less than that in the C group ($P < 0.05$). At T1, the $Q_S/Q_T$ values of groups C, LP, and HP were 29.54 ± 6.89%, 22.66 ± 2.08%, and 19.64 ± 5.76%, respectively, and the $Q_S/Q_T$ values in the LP and HP groups markedly reduced ($P < 0.01$). The surgical field's evaluation by the surgeon among the three groups was not notable ($P > 0.05$).

**CONCLUSION:** CPAP combined with small-tidal-volume ventilation effectively improved arterial oxygenation and reduced $Q_S/Q_T$ and $PaCO_2$ without compromising surgical field exposure during OLV. Among them, 5 $cmH_2O$ CPAP + 60–80 ml TV ventilation had a better effect on improving oxygenation.

## Keywords:

Continuous positive airway pressure, lung surgery, one-lung ventilation, oxygenation, surgical field

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Video-assisted thoracoscopic surgery (VATS) airway management mostly uses one-lung ventilation (OLV) to collapse and isolate the operated lung.[1] However, OLV often leads to intraoperative hypoxemia and postoperative acute lung injury due to intrapulmonary shunting, atelectasis,[2] etc., Lung-protective ventilation strategies (LPVSs),[3,4] such as small tidal volumes (TVs), positive end-expiratory pressure (PEEP), low plateau airway pressure, and low fraction of inspired oxygen ($FiO_2$), are often used in the treatment of OLV to reduce the risk of ventilator-induced lung injury.[5] However, at the same time, low TV may cause alveolar collapse and decrease functional residual air volume due to its low ventilation characteristics. LPVSs lower the safety threshold for hypoxia and limit the available time for physicians to take corrective measures,[6] which can increase the risk of hypoxemia.[7,8] Previous reports have found that the appliance of continuous positive airway pressure (CPAP) to the nondependent lung (NL) can improve the ventilation-to-perfusion ratio (V/Q),[9] weaken inflammatory factor release, and improve patient prognosis,[10] which has been shown to be an emergency strategy after the optimization of ventilation parameters.[3] However, it is the larger pressure values of CPAP that have a more significant effect on oxygenation, and this may interfere with the surgical field. Ventilation of the NL with a low respiratory rate (RR) and small TV is effective in improving oxygenation and increasing alveolar ventilation,[11] and it does not affect the surgical field.

At present, the clinical measures for preventing intraoperative hypoxia are not sufficient. Based on the above situation, we selected patients undergoing thoracoscopic lobectomy as the research participants, applied CPAP with and a low rate and small TV during OLV by connecting a separate ventilator to the NL. At the same time, LPVS was applied in the ventilated lung to compensate for the insufficient improvement in oxygenation caused by CPAP alone or the impact of low ventilation caused by LPVS. This is a prospective, randomized, controlled, and double-blind trial to explore the effects of CPAP combined with small TV ventilation on arterial oxygenation and pulmonary shunt and to minimize the impact of surgical field in order to provide reference for clinical practice.

## Methods

The research program obtained grant permission from the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, No. =2021ER112-1 and registered at http://www.chictr.org.cn (ChiCTR2100050888). All patients have signed an informed consent form.

### Patients

Our study is a single-center, double-blind, randomized-controlled clinical trial. We enrolled 48 patients aged 18–79 years with American Association of Anesthesiologists graded I–III, with forced expiratory volume in 1 s (FEV1) ≥1.5 L, and undergoing VATS lobectomy under OLV at the Affiliated Hospital of North Sichuan Medical College from September 2021 to April 2022. Our exclusion criteria were as follows: conversion to thoracotomy, intraoperative oxygen saturation as low as 85%, previous pneumonectomy, pregnancy, and intubation difficulties.

### Randomization and blinding

Randomly divide patients who meet the conditions and agree to participate into three groups: C group (conventional ventilation, no NL ventilation intervention was performed, $n = 16$), LP group (NL was ventilated with lower CPAP (2 $cmH_2O$) and a 40–60 mL TV, $n = 16$), and HP group (NL was ventilated with higher CPAP (5 $cmH_2O$) and a 60–80 mL TV, $n = 16$). Participants were randomly divided in a 1:1:1 ratio using computer-generated random numbers with a fixed block size of 6. The patient's allocations were sealed in sequentially numbered opaque envelopes which were provided to the principal investigator. The experimental setup was finished before anesthesia induction, the patient's sterile covers was pulled up to hide the anesthesia machine and the separate ventilator. Surgeons, responsible anesthetists, patients, data recorder, and analyzer were blinded about group assignment.

### Study protocol

No preanesthetic medication was taken. Electrocardiogram, noninvasive blood pressure, and pulse oximetry were employed to monitor patients. To assess arterial blood pressure and obtain arterial blood samples for blood gas analysis (BGA), radial artery catheterization proceeds on the opposite side of the lobectomy site used. General anesthesia was caused by an intravenous injection of 0.05 mg/kg midazolam, 0.4–0.5 μg/kg sufentanil, 2.0–2.5 mg/kg propofol, and 0.15–0.25 mg/kg cisatracurium. With the support of the inhalation of 1%–3% sevoflurane, anesthesia was maintained. Using a double-lumen tracheal tube (DLT), intubation was carried out following the induction of anesthesia, 37 Fr for male patients and 35 Fr for female patients. The tube position was confirmed by fiberoptic bronchoscopy. Ultrasound-guided right internal jugular vein puncture and central venous catheterization were performed to sample venous blood for BGA. It is necessary to put a Swan-Ganz catheter into the pulmonary artery to obtain mixed venous blood content; however, due to its complex operation and high invasiveness, we used $ScvO_2$ data obtained from a central venous catheter to determine the pulmonary

shunt index. Generally, their measurement results are similar.[12] Mechanical ventilation was performed with the anesthesia machine (Dräger Fabius plus XL) after endobronchial intubation. After initiating OLV, the patients were divided into the C group, LP group, or HP group at random by drawing an opaque envelope containing a computer-generated sequence number. The NLs of the LP and HP groups were ventilated with a separate ventilator (Mindray, SV300, China), and the NL of the C group was kept open to room air.

Ventilation parameters were as follows: two-lung ventilation (TLV) was carried out in a volume-controlled mode with a TV of 8 mL/kg predicted body weight (PBW), 60% $FiO_2$, PEEP of 4 $cmH_2O$, 1:2 inspiratory-to-expiratory ratio (I: E), and RR of 10–12 per minute. Since OLV was initiated, TV was decreased to 6 mL/kg PBW, RR increased to 12–15 per minute, and other settings were unchanged. After 15 min of OLV, the NLs of the LP and HP groups were ventilated with a separate ventilator. In the LP group, the CPAP pressure value was 2 $cmH_2O$, $FiO_2 = 1$, RR was 5–8 per minute, controlled TV was 40–60 mL, and peak pressure was < 7 $cmH_2O$. The CPAP pressure value of the HP group was 5 $cmH_2O$, $FiO_2 = 1$, RR was 6–10 per minute, controlled TV was 60–80 mL, and the peak pressure was < 10 $cmH_2O$.

When $SaO_2$ decreased to < 90%, the rescue strategies for hypoxia-resistant were started. Fiberoptic bronchoscopy was used to reposition the DLT, the $FiO_2$ of OLV was increased to 1.0, and the NL was subjected to intermittent reinflations. If necessary, ventilation was switched to TLV, and OLV and surgical procedures were performed after hypoxia was corrected. These cases were recorded as study failure.

Every patient was in a lateral position. After the operation, the surgical lungs were expanded again and TLV was restored. At the same time, because the anesthesia machine and the separate ventilator were covered with a sterile cloth. The chief surgeon, who had no knowledge of the ventilation mode being used, was required to make a judgment about the surgical field exposure. All patients completed extubation in the operating room.

## Measurements

Age, gender, body mass index, FEV1, ratio of FEV1 to lung capacity (FEV1/FVC%), duration of surgery, operative region, blood loss, urine volume, postoperative 24-h $SpO_2$, and length of stay were recorded. Each patient's systolic, diastolic, mean arterial blood pressure, heart rate, central venous pressure, pulse oxygen saturation ($SpO_2$), partial pressure of oxygen in alveolar gas ($PAO_2$), alveolar–arterial oxygen pressure gradient (P (A-a) $O_2$), hemoglobin (Hb), $HCO_3^-$, PH, and arterial and mixed venous BGA were recorded at OLV immediate (T0), OLV 30 min (T1), and OLV 60 min (T2). $Q_S/Q_T$ was determined using the intrapulmonary shunting fraction formulas:[13] $Q_S/Q_T = (CcO_2 - CaO_2) / (CcO_2 - CvO_2)$, $CaO_2 = PaO_2 \times 0.0031 + Hb \times 1.36 \times SaO_2$, $CvO_2 = PvO_2 \times 0.0031 + Hb \times 1.36 \times SvO_2$, and $CcO_2 = [FiO_2 \times (PB - PH_2O) - PaCO_2/R] \times 0.0031 + Hb \times 1.36$. $CcO_2$ is the content of pulmonary capillary blood oxygen, $CaO_2$ is the content of arterial blood oxygen, $CvO_2$ is the content of mixed venous blood oxygen, $PvO_2$ is the partial pressure of mixed venous oxygen, $SvO_2$ is the saturation of venous oxygen, PB is the atmospheric pressure (760 mmHg), $PH_2O$ is the 37°C vapor pressure (47 mmHg), and R is the respiratory quotient (0.8).

Records of intraoperative events during surgery, such as $PaO_2 < 80$ mmHg, $SpO_2 < 95\%$, and $PaCO_2 > 45$ mmHg, and cardiovascular events during the operation, were collected. The chief surgeon filled in the satisfaction questionnaire of the surgical field as follows: 0: clear vision, clear organizational structure, and good exposure to the operation field; 0+: the tissue structure is clear and the exposure to the operation field is general; and 1: affecting thoracoscopic operation.

## Statistical analysis

The sample size was worked out depending on the $Q_S/Q_T$ value after OLV 30 min; our preliminary study showed that the average $Q_S/Q_T$ of patients with NL opened to the atmosphere was 25.0% ±6.0%. To detect the 25% difference between any two groups, we calculated a minimum sample size of nine patients per group with an $\alpha$ error of 0.05 and a $\beta$ error of 0.1(PASS.15.0, NCSS, LLC. Kaysville, Utah). Considering possible dropouts, 16 patients were enrolled in each group.

The results are presented as the mean ± standard deviation, medians (interquartile ranges), frequencies, and percentages (%) if applicable. The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. The Fisher's exact test or the Chi-square test was used for categorical data (as appropriate). The Kruskal–Wallis test or the one-way analysis of variance (ANOVA) was used to test continuous variables, depending on the data distribution. Repeated-measures data were analyzed using the two-way repeated-measures ANOVA to appraise the impacts of OLV time, ventilation technology, and interactions. Statistical analyses were achieved using SPSS (version 24.0, USA). $P < 0.05$ was considered the threshold for statistical significance.

# Results

The eligibility of 48 patients was assessed, with three

excluded (one was withdrawn from the study due to low intraoperative oxygen saturation (below 85%) and a change in the $FiO_2$ from 60% to 100%, one was excluded due to intraoperative conversion to open thoracotomy, and one was switched to a single-lumen catheter due to airway stenosis).

The remaining 45 patients undergoing VATS lobectomy completed the research [Figure 1]. Patients' background characteristics, FEV1, FEV1/FVC, and operative region shown in Table 1 were similar in the three groups ($P > 0.05$). During the entire study process, hemodynamic parameters in three groups of patients showed no significant difference ($P > 0.05$). In terms of intraoperative blood loss, intraoperative urine volume, operative time, and postoperative 24-h $SpO_2$ among the three groups, it appeared that no noteworthy variations were found [$P > 0.05$, Table 1].

Intraoperative blood gas values are shown in Table 2. At time point T0, the three groups showed no significant difference in all oxygenation parameters ($P > 0.05$). However, at time point T1, patients in the HP group showed markedly greater $PaO_2$ compared to the C

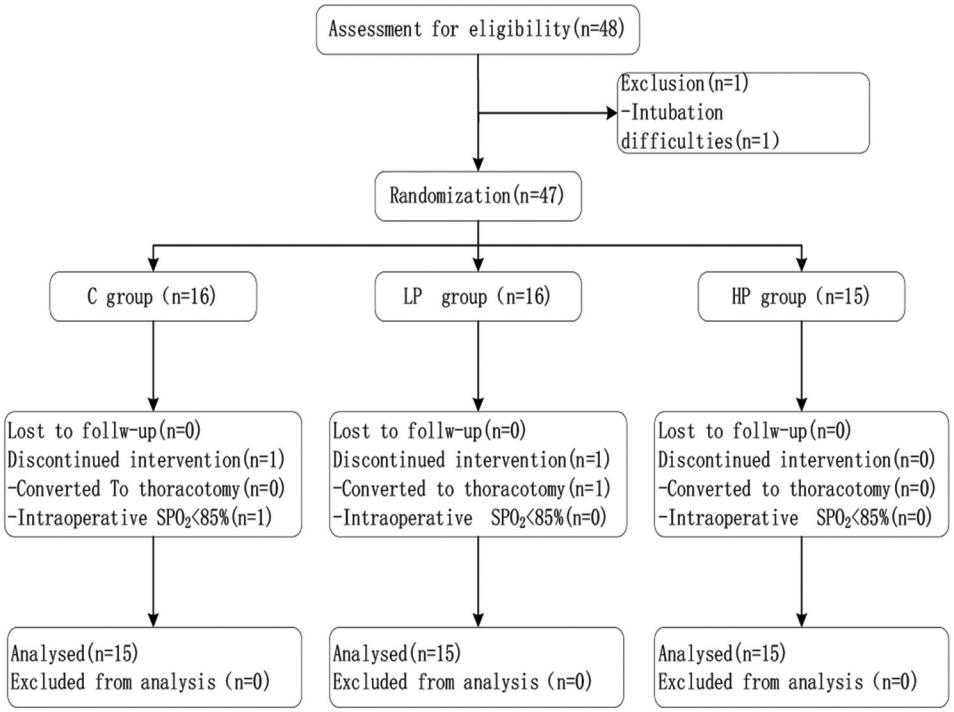


**Figure 1:** Patient flow diagram

**Table 1: Patient characteristics**

| Variables | Group C | Group LP | Group HP |
|---|---|---|---|
| Age (years) | 60.00±11.96 | 60.07±6.27 | 59.87±7.02 |
| Gender (male/female) | 8/7 | 6/9 | 9/6 |
| BMI (kg/m$^2$) | 23.28±2.72 | 23.71±1.78 | 23.90±1.58 |
| Preoperative $FEV_1$ (L) | 2.52±0.71 | 2.47±0.61 | 2.95±0.97 |
| Preoperative $FEV_1$/FVC (%) | 72.37±5.51 | 74.36±5.09 | 73.74±4.85 |
| Operative region (LUL/LLL RUL/RML/RLL) | 5/2/2/2/4 | 5/4/2/2/2 | 6/1/4/2/2 |
| Surgery duration (min) | 160.67±34.36 | 153.67±33.32 | 155.00±26.65 |
| Intraoperative HR (bpm) | 72.91±8.55 | 74.80±9.95 | 71.20±7.82 |
| MAP (mmHg) | 82.28±9.13 | 87.74±7.58 | 90.41±5.52 |
| CVP (mmHg) | 12.73±3.61 | 15.70±16.71 | 13.68±3.25 |
| Blood loss (mL) | 181.00±66.66 | 131.00±55.88 | 158.00±40.30 |
| Urine volume (mL) | 512.33±171.33 | 462.00±110.71 | 438.33±90.65 |
| Postoperative 24-h $SpO_2$ (%) | 98.13±0.92 | 98.47±0.74 | 98.20±0.41 |
| Length of stay (days) | 10.67±4.27 | 10.33±2.44 | 10.93±1.58 |

Values presented as mean±SD, unless specified otherwise. BMI=Body mass index, $FEV_1$=Forced expiratory volume in 1 s, FVC=Forced vital capacity, LLL=Left lower lobe, LUL=Left upper lobe, RLL=Right lower lobe, RML=Right middle lobe, RUL=Right upper lobe, HR=Heart rate, MAP=Mean arterial blood pressure, CVP=Central venous pressure, $SpO_2$=Oxygen saturation

**Table 2: Gas exchange data**

| Variables | Group | T0 | T1 | T2 |
|---|---|---|---|---|
| $PaO_2$ (mmHg) | C | 178.93±75.08 | 92.40±25.41 | 134.47±35.19 |
| | LP | 180.33±61.21 | 115.13±38.76 | 160.13±55.91 |
| | HP | 175.27±51.95 | 152.67±50.71$^{C}$ | 161.87±46.26 |
| $PaCO_2$ (mmHg) | C | 39.93±5.02 | 43.39±4.04 | 44.29±4.14 |
| | LP | 39.87±5.49 | 38.53±5.07$^{C}$ | 38.33±7.08$^{C}$ |
| | HP | 38.47±5.63 | 37.00±3.95$^{C}$ | 37.60±3.48$^{C}$ |
| $SaO_2$ (%) | C | 99.25±0.81 | 96.35±1.52 | 98.59±1.04 |
| | LP | 99.40±0.51 | 98.20±1.26$^{C}$ | 99.07±0.70 |
| | HP | 99.40±0.63 | 98.60±1.45$^{C}$ | 99.20±1.01 |
| $SpO_2$ (%) | C | 99.00±0.65 | 97.27±1.44 | 99.07±1.03 |
| | LP | 99.27±0.46 | 98.73±1.33 | 99.20±1.08 |
| | HP | 99.00±0.65 | 98.80±1.26 | 99.33±1.05 |
| $PAO_2$ (mmHg) | C | 378.88±6.28 | 373.55±5.05 | 372.44±5.17 |
| | LP | 377.97±6.86 | 379.63±6.34$^{C}$ | 379.88±8.85$^{C}$ |
| | HP | 379.72±7.04 | 381.72±4.93$^{C}$ | 380.80±4.35$^{C}$ |
| P (A-a) $O_2$ (mmHg) | C | 199.4±77.37 | 281.36±24.98 | 234.98±34.82 |
| | LP | 197.6±55.92 | 264.50±35.94 | 219.75±51.70 |
| | HP | 204.5±51.01 | 229.25±53.15 | 219.10±49.33 |
| $HCO_3$– (mmol/L) | C | 22.89±1.24 | 23.44±1.12 | 23.19±0.50 |
| | LP | 24.19±2.07 | 23.12±1.17 | 22.09±1.13$^{C}$ |
| | HP | 23.22±0.74 | 21.86±0.86$^{CL}$ | 21.87±0.50$^{C}$ |
| $Q_S/Q_T$ (%) | C | 15.33±6.80 | 29.54±6.89 | 19.95±5.97 |
| | LP | 14.65±5.48 | 22.66±2.08$^{C}$ | 17.14±3.67 |
| | HP | 13.42±3.54 | 19.64±5.76$^{C}$ | 16.12±3.28 |
| Hb (g/dL) | C | 11.35±1.36 | 12.00±1.40 | 11.86±1.54 |
| | LP | 11.93±1.80 | 12.11±1.50 | 11.73±1.70 |
| | HP | 12.34±1.60 | 12.64±1.04 | 12.51±1.14 |
| PH | C | 7.38±0.05 | 7.34±0.04 | 7.33±0.04 |
| | LP | 7.39±0.04 | 7.39±0.05$^{C}$ | 7.38±0.06$^{C}$ |
| | HP | 7.40±0.04 | 7.39±0.03$^{C}$ | 7.38±0.02$^{CL}$ |

$^{C}P$<0.05, compared to the C group, $^{L}P$<0.05, compared to the LP group. The data are presented as the mean±SD. T0 at the start of OLV, T1 at 30 min after the start of OLV, T2 at 60 min after the start of OLV. $PaO_2$=Partial pressure of oxygen in arterial blood, $PaCO_2$=Partial pressure of carbon dioxide in arterial blood, $SaO_2$=Arterial oxygen saturation, $SpO_2$=Oxygen saturation, $PAO_2$=Partial pressure of oxygen in alveolar gas, *P* (A-a) $O_2$=Alveolar–arterial oxygen pressure gradient, $HCO_3$–=Arterial $HCO_3$–, $Q_S/Q_T$=Pulmonary shunt fraction, PH=Arterial PH, Hb=Hemoglobin, SD=Standard deviation

group ($P = 0.013$); the $Q_S/Q_T$ ratios of the three groups were 29.54 ± 6.89%, 22.66 ± 2.08%, and 19.64 ± 5.76%, respectively, and the values in the two groups with CPAP were considerably lower compared to the C group ($P_{LP} = 0.004$, $P_{HP} = 0.002$). At time points T1 through T2, $PaCO_2$ values were significantly lower ($P < 0.05$), while PH and $PAO_2$ values were higher ($P < 0.05$) in both CPAP groups than in the C group. At T2, PH values increased significantly more ($P = 0.017$) in the HP group compared to the LP group. After 30 min of OLV (T1), $HCO_3$ – levels were markedly greater in the HP group compared to both the C and LP groups ($P < 0.05$); and after 60 min of OLV (T2), the decrease in $HCO_3$ – levels increased in the LP group, and $HCO_3$ – levels were lower in both CPAP groups than in the C group ($P < 0.05$). The $SpO_2$ value, *P* (A-a) $O_2$, and Hb content among the three groups of patients did not differ significantly at three time points ($P > 0.05$).

The $PaO_2$ of the C and LP groups reduced significantly after the initiation of OLV (T0), and 60 min after OLV initiation (T2), the $PaO_2$ was increased to exceed that at T1 [$P < 0.05$, Figure 2]. During OLV, the $PaCO_2$ in the C group increased substantially compared to the beginning of OLV ($P_{T1} < 0.05$, $P_{T2} < 0.01$), and the change in $PaCO_2$ over time between the two CPAP groups did not differ markedly [$P > 0.05$, Figure 3].

Four patients (27%) in the C group, one patient (6.7%) in the LP group, and none of the patients in the HP group experienced a drop in their $SpO_2$ values to <95%. Further, one of the patients in the C group presented with $SpO_2$ < 90%. The incidence of $SpO_2$ < 95% differed significantly due to different ventilation strategies used ($P = 0.035$); however, after the Bonferroni correction, the pairwise comparison between groups was not statistically significant ($P_{1/3} > 0.0167$). Forty percent of patients in the C group, 13.3% in the LP group, and 7% in the HP group were found to be at risk of experiencing intraoperative hypoxia (defined as $PaO_2 < 80$ mmHg); the difference in intraoperative hypoxia among the three groups was not apparently meaningful ($P > 0.05$). One of the

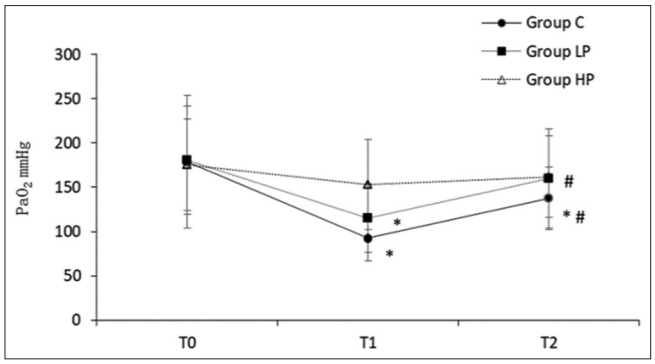


**Figure 2:** Graphical representation of $PaO_2$ at various stages of ventilation. *$P$ < 0.05: compared to the T0; #$P$ < 0.05: compared to the T1

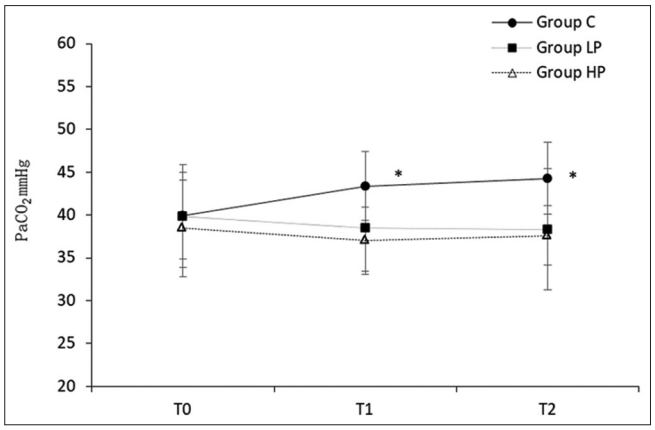


**Figure 3:** Graphical representation of $PaCO_2$ at various stages of ventilation. *$P$ < 0.05: compared to the T0

**Table 3: Intraoperative events and surgical field satisfaction survey**

| Variables | Group C | Group LP | Group HP |
|---|---|---|---|
| $SpO_2$ <95% | 4 | 1 | 0 |
| $PaO_2$ <80 mmHg | 6 | 2 | 1 |
| $PaCO_2$ >45 mmHg | 9 | 5 | 2[C] |
| Evaluation of surgical field conditions (0/0+/1) | 10/5/0 | 9/6/0 | 10/5/0 |

[C]$P$<0.0167, compared to the C group. The data are presented as the number of patients. Evaluation surgical field conditions: 0=Clear vision, clear organizational structure, and good exposure of operation field, 0+=The tissue structure is clear and the exposure of the operation field is general, 1=Affecting thoracoscopic operation, $SpO_2$=Oxygen saturation, $PaCO_2$=Partial pressure of carbon dioxide in arterial blood, $PaO_2$=Partial pressure of oxygen in arterial blood

patients in the C group had $PaO_2$ < 60 mmHg at T1, which did not occur in the CPAP groups. The incidence of intraoperative $PaCO_2$ of more than 45 mmHg in the C group was 60%, compared with 13% in the HP group. The Chi-square test indicated a substantial difference in the occurrence of hypercapnia in the three groups with different ventilation modalities ($\chi^2$ = 7.177, $P$ = 0.034); there was a significant difference between HP and C groups in the post pairwise comparison ($P_{1/3}$ = 0.008). Regarding the surgeon's assessment of interference in the visual field exposure, there was no discernible difference among the three groups ($P$ > 0.05), and there were no patients in the experimental groups who had surgery suspended due to poor visual field exposure conditions [Table 3].

## Discussion

OLV enables the ventilation of one lung while deflating the other. Hypoxemia, the most frequent issue encountered during OLV in thoracic surgery,[7,14] occurs in approximately 4%–10% of patients on OLV.[15] High $FiO_2$ to the dependent lung is no longer suitable for LPVS to avoid hypoxemia, as it increases intrapulmonary shunt and active cluster oxidative stress and aggravates lung injury.[16,17] According to Shuji *et al*.,[17] the hazard of postoperative pulmonary problems rises by about 30% for every 10% increase in oxygen concentration. In addition, the consolidation of small TV and routine PEEP to the dependent lung improved the patient's respiratory function and reduced the occurring rate of postoperative pulmonary complications.[18] Michelet *et al*.[19] found that protective ventilation (5 mL/kg TV + 5 $cmH_2O$ PEEP) had better oxygenation levels and lower interleukin levels than conventional ventilation (9 mL/kg TV + 0 PEEP). Therefore, in this study, a LPVS of the TV at 6 mL/kg 4 $cmH_2O$ PEEP and 60% $FiO_2$ was used on dependent lung ventilation in all patients during OLV.

The ventilation–perfusion mismatch in the NL is a determining factor in the occurrence of hypoxemia during OLV. After the initiation of OLV, the NL is atrophied, alveolar ventilation is abruptly reduced (but blood flow is not), and venous blood (without gas exchange) flows directly back to the left atrium, resulting in a pathological intrapulmonary shunt that impairs arterial oxygenation. Our research found that at T1, compared with the C group, the LP and HP groups resulted in significantly lower $Q_S/Q_T$ in patients ($P$ < 0.01). This CPAP with low-tidal-volume ventilation can effectively reduce pulmonary shunt and achieve the goal of improving oxygenation, which may be related to the application of CPAP to the NL, which can relax collapsed alveoli, reduce the dead space by increasing the surface area of the alveolus, increase alveolar ventilation, and allow more venous blood to participate in gas exchange.[20] Mosing *et al*.[21] stated that the CPAP of 8 $cmH_2O$ utilized in dorsally recumbent horses could reduce the intrapulmonary shunting by 6%–14% during 6 h of anesthesia without affecting the cardiovascular function. Kim *et al*.[22] demonstrated that applying CPAP to the NL during OLV in patients undergoing thoracic surgery can effectively improve $PaO_2$. Low-frequency and low TV pure oxygen ventilation at the NL also can effectively improve oxygenation and insufflate the collapsed lung tissue with oxygen which still has a small part of perfusion, such that the NL can recover part of its

alveolar ventilation,[23] achieving the goal of increasing $PaO_2$ by reducing $PaCO_2$. In addition, pure oxygen inflation of the NL can ventilate the still-expanding alveoli, replacing the air in the alveoli with oxygen, and the pulmonary capillaries absorb the alveolar gas and completely collapse the alveoli. As the alveoli collapse, vascular resistance increases, and abnormal shunted blood flow decreases, allowing for improved arterial oxygen saturation. Shechtman *et al*.[24] showed that compared to CPAP, mini-ventilation to the NL (RR: 8 breaths/minute, TV: 0.1–0.5 L) got a higher pressure of $PaO_2$. Ku *et al*.[25] used two sessions of fiberoptic bronchoscopic segmental oxygen insufflation during OLV, and the $SpO_2$ of patients increased from 86% to more than 90% and remained stable thereafter. In our study, the HP group (5 $cmH_2O$ CPAP + 60–80 mL TV) showed a better effect in enhancing oxygenation. After 30 min of OLV, $PaO_2$ in the HP group (152.6 ± 50.71 mmHg) significantly increased compared to the C group (92.40 ± 25.41 mmHg) ($P < 0.01$), but the difference in the LP group was not significant ($P > 0.05$). After the onset of OLV, both the C group and the LP group had lower PaO2 than T0 at T1, but the degree of decrease in PaO2 in the HP group was significantly lower than that in the C group ($P < 0.05$). This may be due to higher CPAP being more conducive to avoiding alveolar collapse, increasing functional residual air volume, and improving lung compliance, thereby reducing intrapulmonary shunt and improving oxygenation. In addition, higher CPAP reduces airway resistance, maintains better airway opening, and increases ventilation volume. At T1, SaO2 was observed in both experimental groups higher than the control group ($P < 0.01$). Qs/Qt reflects the degree of mixing between pulmonary venous blood and arterial blood, and is a direct manifestation of abnormal pulmonary shunting, and its elevation can directly impair arterial oxygenation. These results indicate that the NL ventilation of CPAP with low tidal volume increased oxygenation and effectively reduced intrapulmonary shunting.

Although it has been suggested[26] that hypoxia during OLV probably does not continue to exacerbate and $PaO_2$ may even spontaneously rebound over time, this may be related to the gradual maximization of hypoxic pulmonary vasoconstriction (HPV).[27] Hypoxic pulmonary arteries produce HPV, which can transport a portion of the diverted blood to the dependent lung, thereby improving a portion of the ventilation-to-perfusion mismatch, which is a self-regulatory mechanism between pulmonary ventilation and pulmonary blood flow. In this study, the $PaO_2$ rebounded in both C and LP groups after 60 min of OLV [Figure 2]. The main mechanism of HPV production is the activation of vasoconstrictors produced in certain parts of the lungs by hypoxia or the inactivation of vasodilators, which indirectly causes pulmonary vasoconstriction and subsequently leads to pulmonary vascular smooth muscle contraction. Therefore, the effect of HPV on improving oxygenation will not immediately take effect, and it is necessary to wait for a period of reaction time. Researches[28,29] discovered that HPV seemed to reach a plateau at 15–45 min and be maximized 4 h after the OLV.[18] For the patient's safety reasons, remedial measures to treat hypoxemia are always required for patients who experience desaturation during OLV. In our study, one (7%) patient in the C group developed hypoxemia ($SpO_2 < 90\%$ or $PaO_2 < 60$ mmHg); however, when considering a broader hypoxia threshold ($PaO_2 < 80$ mmHg), 40% of patients developed hypoxia. Therefore, we still need to take positive measures to prevent the occurrence of intraoperative hypoxia.

The low TV and low platform pressure of LPVS inevitably lead to an increase in $PaCO_2$; this increase in $PaCO_2$ is known as permissive hypercapnia.[30] However, this study found that CPAP combined with small-tidal-volume ventilation mode on the NL can effectively resist the occurrence of this event. In our study, compared with C group, patients in the LP and HP groups had significantly decreased $PaCO_2$ at T1 and T2 [$P < 0.05$, Table 2]. During OLV, the incidence of hypercapnia ($PaCO_2 > 45$ mmHg) in the HP group (13%) was less compared to the C group (60%) [$P_{1/3} = 0.008$, Table 3]. In addition, we found that $HCO_3^-$ exhibited a decreasing trend over time after the commencement of OLV, while $HCO_3^-$ in the C group remained stable during OLV ventilation. Patients in the HP group had significantly less $HCO_3^-$ levels at T1 and T2 than those in the C group. These achievements indicate that CPAP combined with low TV ventilation on the surgical side can effectively reduce $PaCO_2$, improve the metabolism of $CO_2$ in the body, and decrease the incidence of hypercapnia. However, inconsistent with previous studies on the impact of CPAP on OLV,[31,32] the reduction in $PaCO_2$ was statistically significant in our study, which may be related to the small-TV ventilation that accompanied the CPAP input. This might have increased alveolar ventilation, dilated the partially collapsed lungs, and lead to gas exchange again. Recent researches have demonstrated that rather than $CO_2$, acidosis may play a larger role in the therapeutic impact of hypercapnia. Hypercarbonatic acidosis itself can prevent lung injury caused by ischemia–reperfusion;[33] however, a simple increase in $PaCO_2$ can damage gas exchange[34] exacerbating pathological shunts. Feihl *et al*.[34] have found that permissive hypercapnia caused by reducing TV may result in a large increase in pulmonary shunting, although it has no significant impact on the dispersion of ventilation or perfusion. It is generally recommended not to rapidly induce permissive hypercapnia, especially in unstable cardiovascular conditions. Sticher *et al*.[35]

proposed in a clinical study that during OLV in patients undergoing VATS, hypoventilation-induced hypercapnia did not contribute to oxygenation and that hypercapnia could decrease the affinity of hemoglobin for oxygen, thereby reducing the ability of the alveoli to bind oxygen. In thoracic surgery, where the patient's lung function is poor, severe hypercapnia is often accompanied by increased pulmonary vascular resistance; this may exacerbate the decrease in mixed venous and arterial oxygen saturation; thus, maintaining a normal $PaCO_2$ level may result in a more beneficial outcome.

During ventilation, another way to increase oxygenation is to reduce $CO_2$ levels, thereby enhancing alveolar ventilation and increasing oxygenation. According to the partial pressure of oxygen in the alveolar gas ($PAO_2$) formula: $PAO_2 = PIO_2 - PaCO_2/R$; theoretically, alveolar ventilation can be improved by reducing $CO_2$ levels, which can be reflected in this study and can also explain why small-tidal-volume ventilation can achieve superior oxygenation. The findings of this research demonstrate that the LP and HP groups' $PAO_2$ values were greater than the C group's at T1–T2 [Table 2]. Due to the buffering effect of the functional residual capacity on the partial pressure of the gas in the alveoli, the $PAO_2$ values tended to stabilize during ventilation, and in this study, $PAO_2$ values were not affected by the duration of ventilation in all three groups ($P < 0.05$). The alveolar–arterial oxygen difference (P (A-a) $O_2$) is also an index of the pulmonary ventilation function, which can respond sensitively to the alveolar–capillary diffusion function: *P* (A-a) $O_2 = PAO_2 - PaO_2$. The gas exchange between oxygen and blood in the alveoli during pulmonary ventilation is accompanied by oxygen loss; hence, $PaO_2$ must be lower than $PAO_2$. In this study, we found that the mean *P* (A-a) $O_2$ in the HP group was 229.25 ± 53.15 mmHg at T1, which was lesser in comparison to that of the C group, which was 281.36 ± 24.98 mmHg; however, there was not a statistically significant distinction between these two values ($F = 1.223$, $P = 0.31$). The reason for the lack of a significant decrease in *P* (A-a) $O_2$ values in the HP group with significantly decreased $Q_S/Q_T$ and increased $PaO_2$ could be related to the fact that CPAP pressurization of the NL allows more perfusion to the dependent lung, bringing about a decrease in perfusion of NL. To get more evidence to back this up, more research must be done.

For the selection of CPAP pressure, it is unclear how much pressure will be effective, as high-pressure CPAP will affect the exposure of the operating field of vision, which is contrary to the principle of OLV. Per previous studies,[18,22,36] a CPAP of < 10 $cmH_2O$ resulted in only mild lung expansion, which did not interfere with the operating field of vision, but helped surgeons to determine the lung's anatomical structure. Kim *et al*.[22] showed that CPAP with 6 $cmH_2O$ pressure definitely increased $PaO_2$ without the damage of the exposure of operative fields during OLV, while surgical fields were obstructed at a 9-$cmH_2O$ CPAP in 18 patients (90%). El-Tahan *et al*.[31] have found that pressure values of CPAP as low as 2 $cmH_2O$ do not impair surgical exposure.

There is no doubt that delivering a small TV of 100% oxygen ventilation to the NL will greatly improve the oxygen saturation of the patients; however, it is not yet clear how much volume of gas can affect it. Considering that only delivering oxygen to the open arm of the DLT is not beneficial, and a large TV will affect the surgical field of vision, it is necessary to, balancing the relationship between ventilation volume and the surgical field of vision is necessary. Russell[23] believes that adding 400 mL/min of oxygen to the shunted blood is sufficient to make it pass through the arm of the DLT to reach the hypoxic lung tissue; through six equal parts (70 mL), the goal of improving arterial oxygenation can be easily achieved without disturbing the surgical field of vision. Chigurupati *et al*.[26] also confirmed this point by applying intermittent positive pressure ventilation ($FiO_2 = 1$, TV = 70 mL, I: E = 1:10, RR = 6/min) to the surgical lung, effectively improving $PaO_2$ and $SpO_2$ during OLV without the damage of the surgical field. Kremer[33] performed ventilation with a TV of 50 mL in the NL and found that it can effectively improve oxygenation without interfering with the surgical procedures.

Considering the superposition effect of CPAP and low TV ventilation on surgical field exposure, we conservatively selected 2 $cmH_2O$ CPAP + 40–60 mL TV and 5 $cmH_2O$ CPAP + 60–80 mL TV. Our research results show that no surgical field of vision is rated as unsatisfactory, and none of the patients experienced a suspension of the surgical procedure due to visual field interference. Approximately 67% of patients in the C and HP groups met the optimal surgical vision requirements, while 60% of patients in the LP group met the optimal surgical vision requirements. There was no significant difference in surgical field satisfaction. This indicates that there was usually no visual field interference during the operation when using CPAP combined with low TV ventilation in the NL. Specifically, in recent years, the development of robotic-assisted thoracic surgery (RATS) has become increasingly widespread. RATS has a higher magnification and smaller field of view, so the requirements for lung collapse are higher. An early study[37] has found that using CPAP of 5–10 $cmH_2O$ to the NL during OLV in robotic cardiac surgery can improve intraoperative hypoxemia without affecting the surgical field. Another case[38] utilized the CPAP circuit of NL for high-frequency low TV ventilation in RATS, successfully increasing the patient's $SpO_2$ from 87% to 100% without interfering with the surgical field. RATS requires simultaneous OLV and $CO_2$ pneumothorax, and

the mechanism of hypoxemia is more complex and has a higher incidence compared to conventional thoracic surgery;[39] CPAP combined with small-tidal-volume ventilation seems to provide superior oxygenation benefits. However, balancing NL ventilation with the need for optimal lung isolation is a challenge, and more relevant research is needed for further analysis and exploration.

Our study has certain limitations. NL ventilation requires the use of additional equipment, which increases the cost burden and has to some extent hindered clinical promotion. Besides, the evaluation of the surgical field was the subjective decision of a single thoracic surgeon, and there were many factors that could influence this decision, including the technology available to the surgeon, along with the scope and location of the pulmonary resection. Furthermore, we only tested the hemodynamic indexes during the first 60 min of OLV, which was the most frequent time for hypoxemia to appear; however, the measurement of the longer period of OLV could provide us with more information. A multi-center big exponent study is required to further investigate our conclusions.

## Conclusion

During the OLV process of patients undergoing VATS lobectomy, we attempted for the first time to implement CPAP combined with small-tidal-volume ventilation mode by connecting an additional ventilator on the NL. Our study demonstrated that this ventilation mode is simple and feasible, is safe and effective, can improve arterial oxygenation, can reduce intrapulmonary shunting, and has a good effect on the reduction of intraoperative $PaCO_2$ without affecting the surgical field. In clinical practice, this ventilation method can achieve a better oxygenation effect during VATS lobectomy, which has a certain positive significance for formulating a more complete treatment plan. This may serve as a remedial measure to combat hypoxemia during OLV. It may act as a profitable OLV technique, especially for patients with cardiovascular abnormalities who cannot tolerate hypercapnia. However, a multi-center large-sample study is also needed to support the beneficial effect of this ventilation strategy on clinical outcomes.

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## Conflicts of interest
There are no conflicts of interest.

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