



# Effects of different positive end-expiratory pressure titrating strategies on oxygenation and respiratory mechanics during one-lung ventilation: a randomized controlled trial

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**Background:** Positive end-expiratory pressure (PEEP) is widely used to reduce the risk of hypoxemia and atelectasis during one-lung ventilation (OLV); however, the optimal strategy for PEEP titrating remains unclear. The purpose of the study was to investigate the effects of different PEEP titrating strategies on oxygenation and respiratory mechanics during OLV.

**Methods:** Patients undergoing thoracic surgery with general anesthesia were randomly allocated into five groups. In  $P_0$  group, PEEP was set to zero; in  $P_{LIP2}$  group, PEEP was set to 2 cmH<sub>2</sub>O plus the pressure of lower inflection point (LIP) of pressure-volume (P-V) curve; in  $P_{LIP5}$  group, PEEP was titrated to achieve maximum static compliance from the averaged LIP pressure value; in groups  $P_{STAT}$  and  $P_{DYN}$ , the incremental PEEP values were titrated to achieve maximum static compliance or maximum dynamic compliance from 4 cmH<sub>2</sub>O. Hemodynamic measurements, respiratory mechanics, and blood gas analyses were recorded at the beginning of OLV, OLV 15 min, OLV 30 min, OLV 45 min, and OLV 60 min. Also, the intrapulmonary shunt ( $Q_s/Q_t$ ), physiological dead space to tidal volume ratio (VD/VT), and oxygenation index (OI) were calculated and compared.

**Results:** Seventy-five patients consented to participate in this study. Dynamic compliance, peak inspiratory pressure (PIP), and plateau inspiratory pressure ( $P_{plat}$ ) increased after PEEP titration during OLV. PIP,  $Q_s/Q_t$ , and OI showed no differences among groups. Group  $P_{DYN}$  showed lower  $P_{plat}$ , lower driving pressure, and higher dynamic compliance when compared with zero PEEP group.

**Conclusions:** The PEEP titrating strategy according to dynamic compliance can improve respiratory mechanics, whereas it has no significant effects on oxygenation, dead space ratio, and intrapulmonary shunt, suggesting that it is better during OLV for thoracic surgery.

**Keywords:** One-lung ventilation (OLV); positive end-expiratory pressure (PEEP); intrapulmonary shunt; respiratory mechanics

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## Introduction

During one-lung ventilation (OLV) for thoracic surgery, the management of ventilation is still challenging (1). To reduce the risk of atelectasis, hypoxemia, and mismatch of ventilation to perfusion ratio (V/Q), positive end-expiratory pressure (PEEP) is widely used to minimize lung collapse and prevent the alveoli from repeated opening and collapse, and thus improve oxygenation (2,3). However, inappropriate PEEP settings may increase pulmonary vascular resistance and shift blood flow to the non-dependent lung, which can lead to oxygenation impairment during OLV (4). So far, the optimal PEEP level and PEEP titrating strategy during OLV remains to be controversial (1,2,5-8), and processes of maintaining adequate gas exchange and minimizing lung injury may be contradictory at sometimes (9). For seeking the optimal PEEP value, we planned to apply different procedures of PEEP titration, to investigate the effects on oxygenation and respiratory mechanics during OLV.

It has been reported that, when the PEEP value is set to be close to the pressure of lower inflection point (LIP), oxygenation is likely to improve, whereas when the PEEP value increases beyond the pressure of LIP, oxygenation is likely to deteriorate (10). The portion of the pressure-volume (P-V) curve above LIP and below the upper inflection point (UIP) is proposed as the safety zone to avoid cyclic collapse (via setting adequate PEEP) and overdistension (via setting lower VT) (11). However, the intrapulmonary shunt changes during OLV were not considered in previous studies. Furthermore, recent studies have demonstrated that an individualized PEEP adjustment is associated with better oxygenation (2), decreased intrapulmonary shunt (6), lower driving pressure (7), lower or no inflammatory responses (12,13) and lower incidence of postoperative pulmonary complications (14,15). Conversely, an individualized PEEP titration, will not completely prevent atelectasis formation in the particular population (16,17). Thus, we presumed whether there was an optimal pressure between the pressure of LIP and UIP that would keep the optimal amount of alveoli open, and improve oxygenation, intrapulmonary shunt, or respiratory mechanics during OLV.

Therefore, we conducted a randomized controlled trial for OLV in thoracic surgery and compared clinical measurements among PEEP titration groups. Our study aimed to investigate which PEEP titrating method during OLV can improve oxygenation and respiratory mechanics. Thus, we applied different PEEP titrating strategies and

measured hemodynamic parameters, respiratory mechanics, intrapulmonary shunt, dead space to tidal volume ratio, and oxygenation index (OI) in patients undergoing thoracic surgery during OLV. We present the following article in accordance with the CONSORT reporting checklist (available at <http://dx.doi.org/10.21037/apm-19-441>).

## Methods

### *Study design and populations*

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of Shanghai General Hospital (No. 2016KY109) and registered at the [chictr.org.cn](http://www.chictr.org.cn) website (ChiCTR-OPC-16008292). The study was performed from January 2015 to January 2016 in the Department of Anesthesiology, Shanghai General Hospital. Written informed consent was obtained from all patients before surgery.

Patients scheduled for elective pulmonary resection or esophagectomy under general anesthesia were enrolled if they were aged 18–70 years with American Society of Anesthesiologists (ASA) physical status I or II. The exclusion criteria were body mass index (BMI) <20 or >28 kg/m<sup>2</sup>, acute pulmonary infection, uncompensated cardiac disease, or a preoperative pulmonary function test of forced expiratory volume in the first second (FEV<sub>1</sub>) <60% of the predictive value. Drop-out criteria were intraoperative bleeding more than 500 mL, severe hypoxemia, or severe hemodynamic instability during the operation.

Patients were randomly allocated to one of five groups: the “zero PEEP” group (P<sub>0</sub>, as the control group), the “PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve” group (P<sub>LIP2</sub>), the “PEEP titration according to LIP of P-V curve” group (P<sub>LIPS</sub>), the “PEEP titration according to static compliance” group (P<sub>STAT</sub>), or the “PEEP titration according to dynamic compliance” group (P<sub>DYN</sub>). The intraoperative mechanical ventilation procedure was performed according to group assignment.

### *Anesthesia management*

Anesthesia management and intraoperative care were standardized. After transferred to the operating room, patients were monitored for electrocardiography, pulse oximetry, and noninvasive blood pressure measurements using an S/5 monitor (Datex-Ohmeda, GE, Finland). For

hemodynamic measurements and blood sampling, a 20-G radial artery catheter was introduced under local anesthesia with lidocaine, which was flushed using a pressure bag with 500 mL of heparinized saline dilution. Also, a 14-G right internal jugular vein catheter was placed under local anesthesia with lidocaine. Blood gas values were determined by a blood gas analyzer (ABL 80, Radiometer, Denmark).

After 5 minutes of facemask preoxygenation (100% oxygen), anesthesia was induced with midazolam 0.1 mg/kg, fentanyl 4 µg/kg, propofol 1.5–2 mg/kg, and rocuronium 0.6 mg/kg. After the patients were anesthetized, tracheal intubation was conducted with an appropriate double-lumen tube (Shiley™ Endobronchial Suction Catheters with Color Coded Connectors, Covidien, Ireland). The tube position was confirmed by visual bronchoscopy in the supine and lateral positions. Sevoflurane inhalation was administered to maintain the minimal alveolar concentration (MAC) between 1.0 and 1.2. Additional fentanyl (50 µg each time) and rocuronium (10 mg each time) were administered as necessary.

### Ventilation settings

Pulmonary ventilation in all patients was supported by the anesthesia machine (WATO EX-55, Mindray, China) using volume-controlled ventilation mode. The inspiratory-to-expiratory ratio was 1:1.5, and the frequency was adjusted to maintain end-tidal carbon dioxide partial pressure (PetCO<sub>2</sub>) between 35 and 50 mmHg. During two-lung ventilation (TLV), all patients of five groups were ventilated with the same protocol (VT: 8 mL/kg, FiO<sub>2</sub>: 60%, and PEEP: 0). During OLV, VT was set to 6 mL/kg, FiO<sub>2</sub> was set as 100% to avoid hypoxemia and exclude interference in the measurement of PaO<sub>2</sub>, and PEEP varied according to the experimental protocol (see PEEP titrating strategies). After OLV switched to TLV and before extubation, the bilateral lung of all patients was treated with sustained manual expansion of the reservoir bag (30 cmH<sub>2</sub>O for 10 seconds) three times.

### PEEP titrating strategies

In the five groups, the same procedures were applied except for the PEEP titration of the OLV period (Figure 1). During the TLV period, the P-V curve was measured in the lateral position by the GE E-sCAiOVX respiratory module and determined three times, and then the mean value of the

LIP pressure of the P-V curve was recorded. In P<sub>LIP2</sub> group, the PEEP value during OLV was set to 2 cmH<sub>2</sub>O above the pressure of LIP; in P<sub>LIP5</sub> group, taking the averaged value of the LIP pressure as fundamental titration value, we gradually increased PEEP value during OLV in 1 cmH<sub>2</sub>O steps until static compliance was achieved to the maximum, while PEEP was held at each step for 5 minutes; in group P<sub>STAT</sub>, the incremental PEEP value during OLV was titrated to achieve maximum static compliance in 1 cmH<sub>2</sub>O steps and held at each step for 5 minutes; in group P<sub>DYN</sub>, the incremental PEEP value during OLV was titrated to achieve maximum dynamic compliance from 4 cmH<sub>2</sub>O in 1 cmH<sub>2</sub>O steps and held at each step for 5 minutes; in P<sub>0</sub> group, zero PEEP level was set as control.

### Measurements

The heart rate (HR), mean arterial pressure (MAP), pulse oxygen saturation (SpO<sub>2</sub>), PetCO<sub>2</sub>, VT, respiratory rate (RR), peak inspiratory pressure (PIP), plateau inspiratory pressure (P<sub>plat</sub>), and I: E were monitored continuously with an S/5 monitor (Datex-Ohmeda, Finland). The gas sampling tube (sidestream technique) was connected to the Y-junction of the respiratory circuit. Each measurement was obtained and recorded immediately at the beginning of OLV (T0), OLV 15 min (T1), OLV 30 min (T2), OLV 45 min (T3), and OLV 60 min (T4). Arterial and venous blood samplings were performed for blood gas analyses at T0, T1, T2, T3, and T4, then arterial carbon dioxide partial pressure (PaCO<sub>2</sub>), arterial oxygen partial pressure (PaO<sub>2</sub>), arterial oxygen saturation (SaO<sub>2</sub>), and venous oxygen saturation (SvO<sub>2</sub>) were recorded.

Driving pressure was calculated using the equation (18):

$$\Delta P = P_{\text{plat}} - \text{PEEP} \quad [1]$$

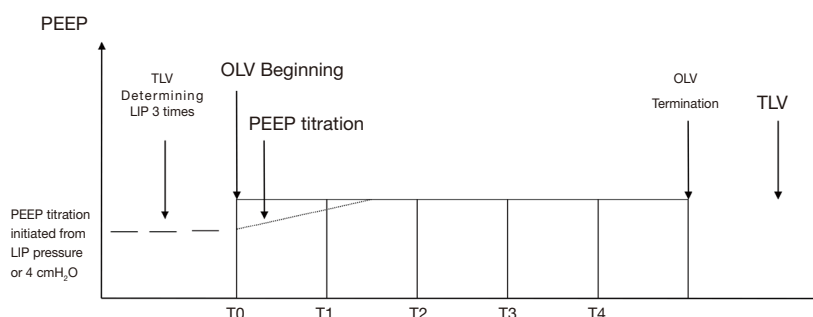
Dynamic compliance of the respiratory system was calculated with the standard formula:

$$C = \text{VT}/(\text{PIP} - \text{PEEP}) \quad [2]$$

The alveolar dead space/tidal volume ratio (VD/VT) was calculated using the equation (19):

$$\text{VD}/\text{VT} = 1.14 \times (\text{PaCO}_2 - \text{PetCO}_2)/\text{PaCO}_2 - 0.005 \quad [3]$$

The intrapulmonary shunt (Qs/Qt) was calculated with



**Figure 1** PEEP titration of OLV period. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. PEEP, positive end-expiratory pressure; OLV, one-lung ventilation; TLV, two-lung ventilation; LIP, lower inflection point.

the formula (see [Supplement I](#)).

### Sample size and randomization

Based on our pilot study, it was estimated that a total of 75 patients were needed to detect a difference of at least a 20% difference in PaO<sub>2</sub> between any study group and the control group at the time of OLV 30 min, with a 5% significance level, 80% power. Sample size analysis was performed using PASS software (version 11.0.7, NCSS, USA).

Randomization was done by computer-generated random numbers (randomization lists). The patients were randomly assigned with a 1:1:1:1:1 ratio to one of the five groups: P<sub>LIP2</sub>, P<sub>LIPS</sub>, P<sub>STAT</sub>, P<sub>DYN</sub>, or P<sub>0</sub> group. The randomization schedule was generated by NCSS PASS software (see [Supplement II](#)) and concealed from the investigators. The administrator prepared sequentially numbered envelopes that were sealed and opaque to maintain allocation concealment until the time of randomization. The investigators enrolled the study subjects after evaluating eligibility and assigned patients to different groups by opening the randomization envelopes just before the beginning of anesthesia.

### Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows (version 20.0, IBM, USA). Continuous data were evaluated with the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as means ± standard deviation. Nonnormally distributed continuous variables were presented using medians (range). Differences between measurements at each time point using different PEEP titrating strategies were analyzed with multivariate

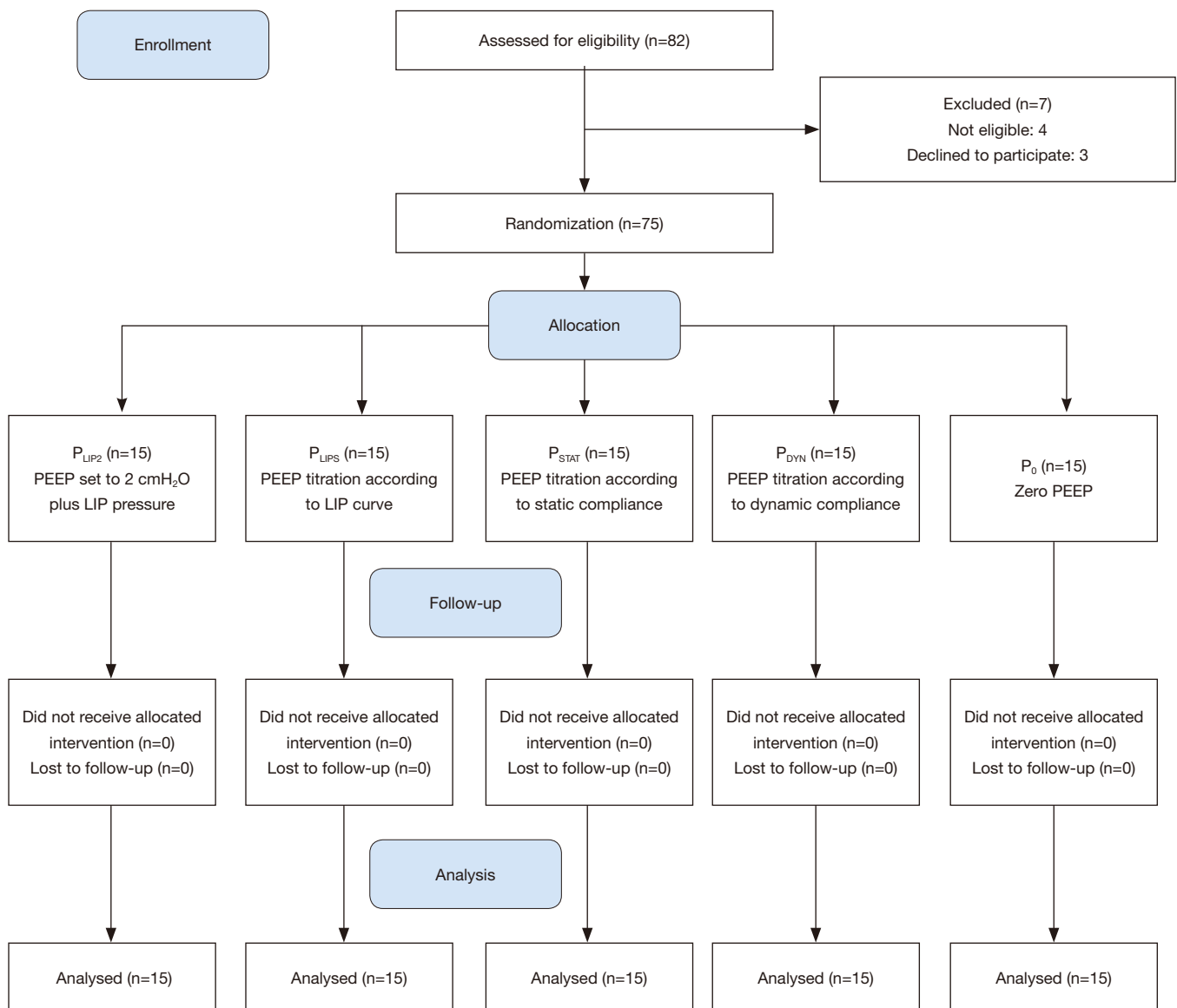
ANOVA (General Linear Model), while post hoc analyses were performed using Bonferroni's correction. Categorical data were presented as frequencies and analyzed with a  $\chi^2$  test. We considered a value of P<0.05 to be statistically significant.

### Results

Eighty-two patients were assessed for eligibility in this study. Seventy-five patients consented to participate in this study and were randomly assigned to groups ([Table S1](#)). Finally, 15 patients in each group were analyzed ([Figure 2](#)). None of the patients demonstrated protocol-related complications or adverse events, such as intraoperative bleeding more than 500 mL, severe hypoxemia during OLV, or severe hemodynamic instability during the operation. None of the patients was affected by severe postoperative pulmonary complications. There were no significant differences in patients' characteristics and clinical data among the five groups ([Table 1](#)).

Comparisons of hemodynamic measurements are presented in [Table 2](#). During OLV, MAP decreased at every time point when compared with the baseline value. In P<sub>LIP2</sub> and P<sub>STAT</sub> group, there were significant differences at T1 and T2 when compared with T0. In the P<sub>LIPS</sub> group, MAP decreased significantly at T1, T2, T3, and T4 when compared with T0.

Comparisons of respiratory mechanics are presented in [Table 3](#). PIP and P<sub>plat</sub> significantly increased after PEEP titration when compared with the basal levels at T0 (P<0.05). PIP showed no differences among groups despite the different PEEP strategies. In groups P<sub>LIP2</sub>, P<sub>LIPS</sub>, and P<sub>STAT</sub>, P<sub>plat</sub> significantly increased after PEEP titration when compared with group P<sub>0</sub> (P<0.05). P<sub>plat</sub> in group P<sub>DYN</sub>



**Figure 2** The consort flow diagram. PEEP, positive end-expiratory pressure; LIP, lower inflection point; P-V, pressure-volume;  $P_{LIP2}$ , “PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group;  $P_0$ , “zero PEEP” group, as the control group.

showed no differences compared to  $P_0$  ( $P>0.05$ ). In each PEEP titration group, the PEEP values at T4 were close ( $P_{LIP2}$ ,  $7.7\pm 0.8$ ;  $P_{LIPS}$ ,  $8.1\pm 0.7$ ;  $P_{STAT}$ ,  $7.5\pm 1.2$ ;  $P_{DYN}$ ,  $7.7\pm 0.7$ ;  $P>0.05$ ).

Comparisons of driving pressure are presented in *Figure 3*. Driving pressure significantly decreased after PEEP titration when compared with the basal levels at

T0 ( $P<0.05$ ). In group  $P_{DYN}$ , driving pressure significantly decreased after PEEP titration when compared with group  $P_0$  ( $P<0.05$ ).

Comparisons of dynamic compliance are presented in *Figure 4*. Dynamic compliance significantly increased after PEEP titration when compared with the basal levels at T0 ( $P<0.05$ ). In group  $P_{LIP2}$ ,  $P_{STAT}$ , and  $P_{DYN}$ , dynamic

**Table 1** Patients' characteristics and clinical data

Characteristics and clinical data	P <sub>LIP2</sub> (n=15)	P <sub>LIPS</sub> (n=15)	P <sub>STAT</sub> (n=15)	P <sub>DYN</sub> (n=15)	P <sub>0</sub> (n=15)
Male/female	9/6	8/7	8/7	9/6	9/6
Age (yr)	58±7	57±9	62±6	59±8	57±10
BMI (kg/m <sup>2</sup> )	23.9±1.8	23.9±2.8	22.5±2.4	21.7±5.8	23.7±2.2
ASA (I/II)	4/11	5/10	3/12	4/11	3/12
Preoperative FEV1 (% of predicted)	85.2±9.8	87.4±9.0	87.3±8.8	86.9±9.2	87.1±9.3
Preoperative hemoglobin (g/dL)	11.8±1.3	11.9±1.6	12.5±1.3	12.5±1.5	13.0±2.0
Preoperative PaO <sub>2</sub> (mmHg)	86.5±14.7	87.9±19.6	89.0±17.5	88.2±15.6	86.7±18.2
Preoperative PaCO <sub>2</sub> (mmHg)	42.5±4.6	43.1±4.2	42.1±5.0	41.9±4.8	43.6±5.4
Type of surgery (esophagus/lung)	3/12	5/10	4/11	4/11	5/10
Duration of OLV (min)	135 [81, 186]	140 [85, 200]	132 [91, 181]	139 [85, 193]	145 [98, 203]
Intraoperative bleeding (mL)	130 [50, 200]	150 [50, 250]	155 [50, 250]	125 [50, 200]	140 [50, 220]

Data are presented as means ± standard deviation, or the number of patients. PEEP, positive end-expiratory pressure; LIP, lower inflection point; P-V, pressure-volume; P<sub>LIP2</sub>, "PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve" group; P<sub>LIPS</sub>, "PEEP titration according to LIP of P-V curve" group; P<sub>STAT</sub>, "PEEP titration according to static compliance" group; P<sub>DYN</sub>, "PEEP titration according to dynamic compliance" group; P<sub>0</sub>, "zero PEEP" group, as the control group; BMI, body mass index; ASA, American Society of Anesthesiologists physical status; FEV1, forced expiratory volume in the first second; PaO<sub>2</sub>, arterial oxygen partial pressure; PaCO<sub>2</sub>, arterial carbon dioxide partial pressure; OLV, one-lung ventilation.

**Table 2** Comparisons of hemodynamic measurements

Groups	Measurements	T0	T1	T2	T3	T4
P <sub>LIP2</sub>	MAP (mmHg)	84.6±12.4	74.3±11.3*	74.6±11.7*	77.7±11.7	79.4±9.6
	HR (beats/min)	72.5±12.9	70.9±11.9	69.1±11.3	69.9±10.6	70.7±9.9
P <sub>LIPS</sub>	MAP (mmHg)	82.6±13.5	74.5±11.6*	71.6±13.2*	69.8±10.6*	74.3±10.3*
	HR (beats/min)	74.6±13.8	77.6±9.6	78.1±9.4	75.3±9.6	77.88±9.1
P <sub>STAT</sub>	MAP (mmHg)	84.6±14.6	73.5±9.1*	76.4±11.1*	78.4±10.0	79.8±10.9
	HR (beats/min)	72.9±14.8	71.5±13.8	71.5±13.8	69.2±16.0	68.5±15.0
P <sub>DYN</sub>	MAP (mmHg)	79.6±14.1	73.9±11.4	73.9±11.2	72.9±11.2	74.7±7.8
	HR (beats/min)	78.5±5.2	77.7±8.0	77.5±7.0	75.1±10.1	75.1±9.3
P <sub>0</sub>	MAP (mmHg)	92.3±17.2	79.8±14.1	81.5±12.1	82.0±13.8	82.7±14.2
	HR (beats/min)	72.5±12.4	70.9±12.3	70.4±13.9	70.7±12.0	70.7±12.0

Data are presented as means ± standard deviation. \*, P<0.05 as compared to T0 within the group. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. PEEP, positive end-expiratory pressure; LIP, lower inflection point; P-V, pressure-volume; P<sub>LIP2</sub>, "PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve" group; P<sub>LIPS</sub>, "PEEP titration according to LIP of P-V curve" group; P<sub>STAT</sub>, "PEEP titration according to static compliance" group; P<sub>DYN</sub>, "PEEP titration according to dynamic compliance" group; P<sub>0</sub>, "zero PEEP" group, as the control group; HR, heart rate; MAP, mean arterial pressure.

compliance significantly increased after PEEP titration when compared with group P<sub>0</sub> (P<0.05).

Comparisons of VD/VT are presented in *Figure 5*. VD/

VT significantly increased in group P<sub>LIP2</sub> at T1 and T2, and in group P<sub>LIPS</sub> at T3 and T4 when compared with T0 (P<0.05). However, VD/VT did not change significantly in



**Table 3** Comparisons of respiratory mechanics

Groups	Measurements	T0	T1	T2	T3	T4 <sup>§</sup>
P <sub>LIP2</sub>	PIP (cmH <sub>2</sub> O)	19.4±3.4	21.8±2.5	21.9±2.6	22.1±2.2	22.4±2.4*
	P <sub>plat</sub> (cmH <sub>2</sub> O)	15.9±5.2	18.5±3.7 <sup>#</sup>	18.9±3.9 <sup>#</sup>	18.9±3.9 <sup>#</sup>	19.0±4.2 <sup>#</sup>
	PEEP (cmH <sub>2</sub> O)	0	7.7±0.8	7.7±0.8	7.7±0.8	7.7±0.8
P <sub>LIPS</sub>	PIP (cmH <sub>2</sub> O)	20.1±3.6	22.7±1.6	24.0±2.3*	24.0±2.5*	23.9±2.0*
	P <sub>plat</sub> (cmH <sub>2</sub> O)	17.7±3.5	20.6±1.5* <sup>#</sup>	19.7±3.3* <sup>#</sup>	21.4±2.6* <sup>#</sup>	21.5±2.2* <sup>#</sup>
	PEEP (cmH <sub>2</sub> O)	0	7.3±1.0	8.1±0.6	8.1±0.6	8.1±0.7
P <sub>STAT</sub>	PIP (cmH <sub>2</sub> O)	18.9±3.7	21.2±3.6	22.4±3.4	22.5±3.4	22.8±3.6*
	P <sub>plat</sub> (cmH <sub>2</sub> O)	16.5±3.4	18.6±3.4 <sup>#</sup>	19.7±3.3 <sup>#</sup>	19.8±3.2 <sup>#</sup>	20.2±3.7 <sup>#</sup>
	PEEP (cmH <sub>2</sub> O)	0	6.1±0.5	7.5±0.8	7.5±1.2	7.5±1.2
P <sub>DYN</sub>	PIP (cmH <sub>2</sub> O)	21.8±2.2	23.3±1.7	24.0±1.6*	24.1±1.6*	23.9±1.7*
	P <sub>plat</sub> (cmH <sub>2</sub> O)	10.1±4.6	13.4±3.9	14.7±3.8*	19.8±3.2*	14.4±3.5
	PEEP (cmH <sub>2</sub> O)	0	6.0±0.1	7.7±0.7	7.7±0.7	7.7±0.7
P <sub>0</sub>	PIP (cmH <sub>2</sub> O)	20.7±3.6	21±3.8	21.3±3.5	21.9±3.3	21.9±4.9
	P <sub>plat</sub> (cmH <sub>2</sub> O)	13.9±4.9	14.4±4.7	14.3±4.6	14.8±4.7	14.3±4.5
	PEEP (cmH <sub>2</sub> O)	0	0	0	0	0

Data are presented as means ± standard deviation. <sup>§</sup>, because of different PEEP titrating procedures, PEEP levels were compared only at T4 among groups P<sub>LIP2</sub>, P<sub>LIPS</sub>, P<sub>STAT</sub>, and P<sub>DYN</sub>; \*, P<0.05 as compared to T0 within the group; <sup>#</sup>, P<0.05 as compared to the P<sub>0</sub> group. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. PEEP, positive end-expiratory pressure; LIP, lower inflection point; P-V, pressure-volume; P<sub>LIP2</sub>, “PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve” group; P<sub>LIPS</sub>, “PEEP titration according to LIP of P-V curve” group; P<sub>STAT</sub>, “PEEP titration according to static compliance” group; P<sub>DYN</sub>, “PEEP titration according to dynamic compliance” group; P<sub>0</sub>, “zero PEEP” group, as the control group; PIP, peak inspiratory airway pressure; P<sub>plat</sub>, plateau airway pressure.

group P<sub>DYN</sub>.

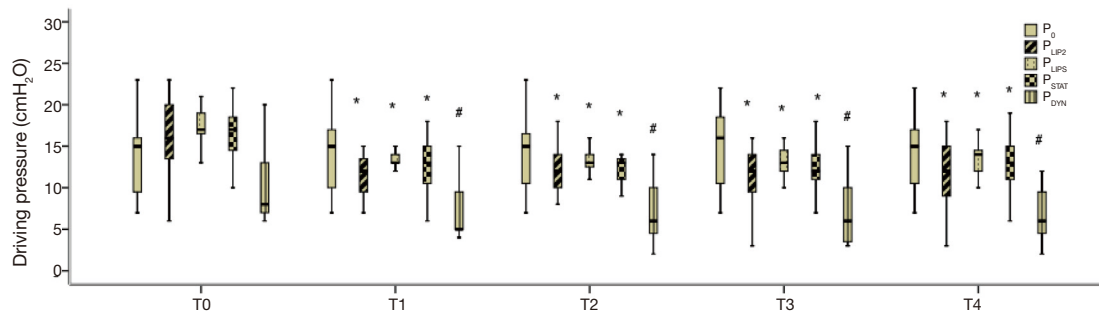
Comparisons of Qs/Qt and OI are presented in *Figure 6* and *Figure 7*. After PEEP titration, there was a slight decrease in Qs/Qt during OLV. However, there were no significant changes at T1, T2, T3, and T4 when compared with T0 in any group. There were no significant changes in groups P<sub>LIP2</sub>, P<sub>LIPS</sub>, P<sub>STAT</sub>, and P<sub>DYN</sub> when compared with group P<sub>0</sub>.

## Discussion

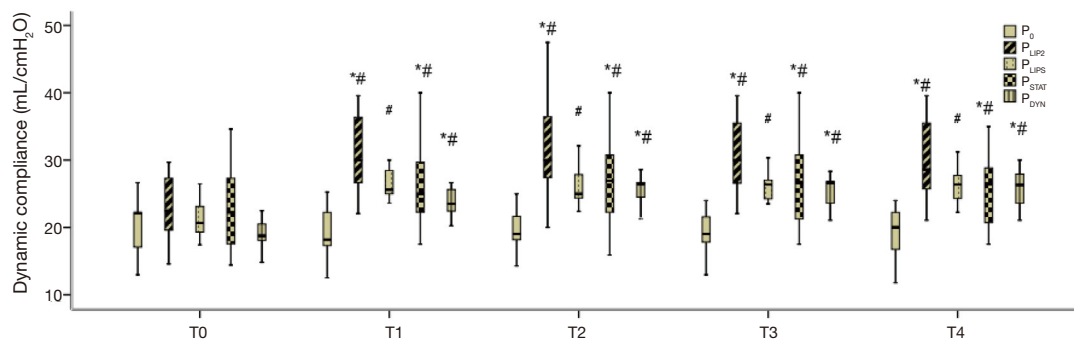
Our study demonstrated that dynamic compliance, VD/VT, PIP, and P<sub>plat</sub> significantly increased, and driving pressure significantly decreased after PEEP titration when compared with the basal levels, whereas the intrapulmonary shunt and OI showed no significant changes. PIP, Qs/Qt, and OI showed no differences among groups despite the different PEEP titrating strategies. The optimal PEEP values were

close in each PEEP titration group. When PEEP titrated according to dynamic compliance, respiratory mechanics showed lower P<sub>plat</sub>, lower driving pressure, and higher dynamic compliance, while the intrapulmonary shunt, dead space ratio, and OI did not change significantly.

A low tidal volume ventilation strategy combined with PEEP, as an essential component of a protective lung ventilation protocol, can prevent ventilator-induced lung injury (VILI). The mechanism of PEEP involves maintaining alveoli open at the end of expiration, improving functional residual capacity, lung compliance, and oxygenation, and decreasing intrapulmonary shunt (2,3). In clinical studies, PEEP is most commonly set near to the pressure of LIP of the P-V curve to prevent end-expiratory collapse (10). Although this seems to be physiological, its clinical application value is still unclear and controversial. First of all, the pressure of LIP is hard to be defined on the P-V curve, especially in the existence



**Figure 3** Comparisons of driving pressure among groups  $P_{LIP2}$ ,  $P_{LIPS}$ ,  $P_{STAT}$ ,  $P_{DYN}$ , and  $P_0$  at T1, T2, T3, T4, and T0. Box and whisker plot showing changes in driving pressure during OLV in the lateral position among  $P_0$  group (blank box),  $P_{LIP2}$  (diagonally shaded box),  $P_{LIPS}$  group (dotted box),  $P_{STAT}$  group (mosaic box), and  $P_{DYN}$  group (vertically lined box). The boxes represent the interquartile range (25–75%), the horizontal line within the boxes represents the median, and whiskers represent 10–90% error bars. \*,  $P < 0.05$  as compared to T0 within the group; #,  $P < 0.05$  as compared to the  $P_0$  group. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. PEEP, positive end-expiratory pressure;  $P_0$ , “zero PEEP” group, as the control group;  $P_{LIP2}$ , “PEEP set to 2  $\text{cmH}_2\text{O}$  above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group; OLV, one-lung ventilation; LIP, lower inflection point; P-V, pressure-volume.

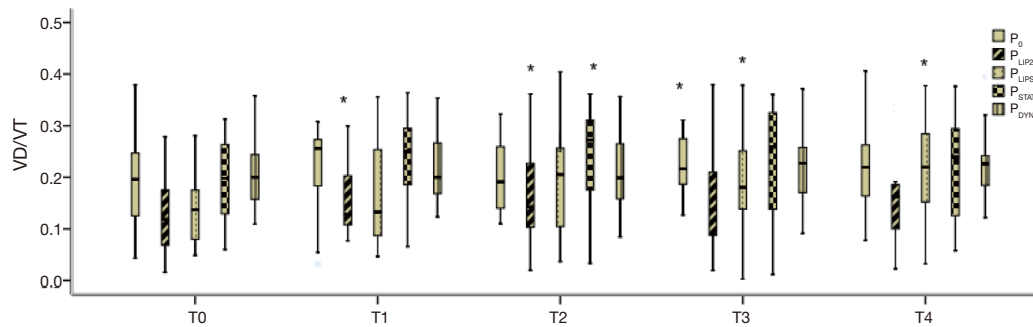


**Figure 4** Comparisons of dynamic compliance among groups  $P_{LIP2}$ ,  $P_{LIPS}$ ,  $P_{STAT}$ ,  $P_{DYN}$ , and  $P_0$  at T0, T1, T2, T3, and T4. Box and whisker plot showing changes in dynamic compliance during OLV in the lateral position among  $P_0$  group (blank box),  $P_{LIP2}$  (diagonally shaded box),  $P_{LIPS}$  group (dotted box),  $P_{STAT}$  group (mosaic box), and  $P_{DYN}$  group (vertically lined box). The boxes represent the interquartile range (25–75%), the horizontal line within the boxes represents the median, and whiskers represent 10–90% error bars. \*,  $P < 0.05$  as compared to T0 within the group; #,  $P < 0.05$  as compared to the  $P_0$  group. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. PEEP, positive end-expiratory pressure;  $P_0$ , “zero PEEP” group, as the control group;  $P_{LIP2}$ , “PEEP set to 2  $\text{cmH}_2\text{O}$  above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group; OLV, one-lung ventilation; LIP, lower inflection point; P-V, pressure-volume.

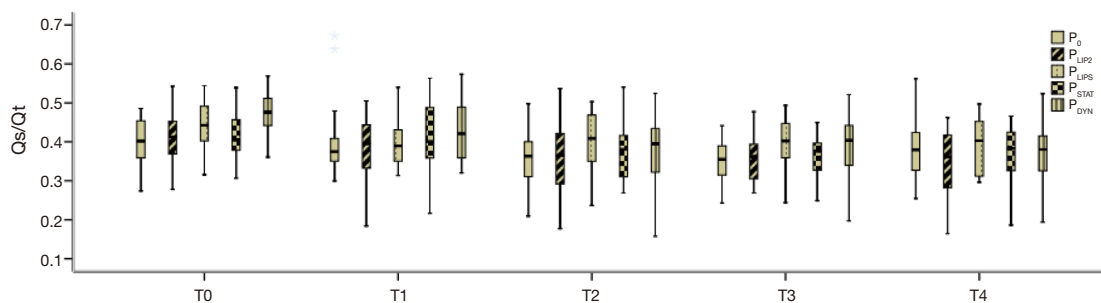
of extensive lung lesions. Secondly, the gravity gradient of pleural pressure in patients implies that there will not be a single pressure open up collapsed regions of the recruitable lung. Lastly, the approach of P-V curve analysis may be

affected by observers’ variability, which makes it difficult to compare results from different studies. Therefore, there is no standard method for PEEP titration individualized according to LIP. For group  $P_{LIP2}$ , we intended to decide





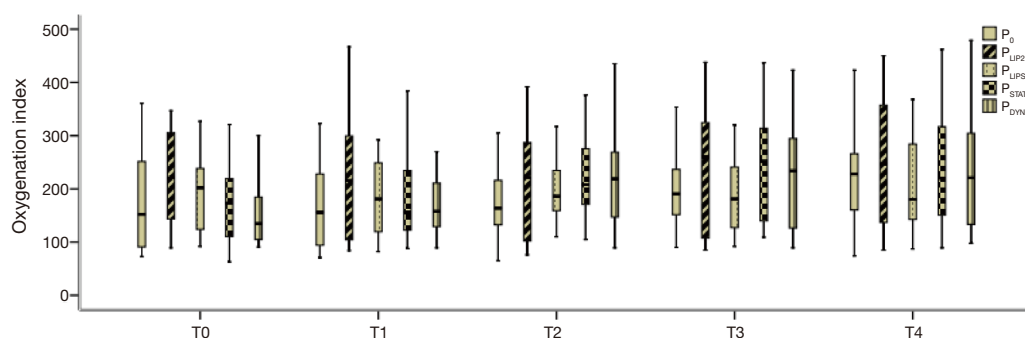
**Figure 5** Comparisons of  $VD/VT$  among groups  $P_{LIP2}$ ,  $P_{LIPS}$ ,  $P_{STAT}$ ,  $P_{DYN}$ , and  $P_0$  at T1, T2, T3, T4, and T0. Box and whisker plot showing changes in  $VD/VT$  during OLV in the lateral position among  $P_0$  group (blank box),  $P_{LIP2}$  (diagonally shaded box),  $P_{LIPS}$  group (dotted box),  $P_{STAT}$  group (mosaic box), and  $P_{DYN}$  group (vertically lined box). The boxes represent the interquartile range (25–75%), the horizontal line within the boxes represents the median, and whiskers represent 10–90% error bars. \*,  $P < 0.05$  as compared to T0 within the group. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min.  $V_D/V_T$ , dead space/tidal volume ratio; PEEP, positive end-expiratory pressure;  $P_0$ , “zero PEEP” group, as the control group;  $P_{LIP2}$ , “PEEP set to 2  $\text{cmH}_2\text{O}$  above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group; OLV, one-lung ventilation; LIP, lower inflection point; P-V, pressure-volume.



**Figure 6** Comparisons of  $Qs/Qt$  among groups  $P_{LIP2}$ ,  $P_{LIPS}$ ,  $P_{STAT}$ ,  $P_{DYN}$ , and  $P_0$  at T1, T2, T3, T4, and T0. Box and whisker plot showing changes in  $Qs/Qt$  during OLV in the lateral position among  $P_0$  group (blank box),  $P_{LIP2}$  (diagonally shaded box),  $P_{LIPS}$  group (dotted box),  $P_{STAT}$  group (mosaic box), and  $P_{DYN}$  group (vertically lined box). The boxes represent the interquartile range (25–75%), the horizontal line within the boxes represents the median, and whiskers represent 10–90% error bars. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min.  $Qs/Qt$ , intrapulmonary shunt; PEEP, positive end-expiratory pressure;  $P_0$ , “zero PEEP” group, as the control group;  $P_{LIP2}$ , “PEEP set to 2  $\text{cmH}_2\text{O}$  above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group; OLV, one-lung ventilation; LIP, lower inflection point; P-V, pressure-volume.

a point of P-V curve between LIP and UIP according to our clinical experience and previous studies (11). For group  $P_{LIPS}$ , we gradually increased PEEP value from the basal LIP pressure until static compliance achieved maximum

value. PEEP titration according to LIP (group  $P_{LIP2}$  and  $P_{LIPS}$ ), showed no significant changes in the intrapulmonary shunt and not improved oxygenation. However, the dead space ratio significantly increased when compared with the



**Figure 7** Comparisons of OI among groups  $P_{LIP2}$ ,  $P_{LIPS}$ ,  $P_{STAT}$ ,  $P_{DYN}$ , and  $P_0$  at T1, T2, T3, T4, and T0. Box and whisker plot showing changes in OI during OLV in the lateral position among  $P_0$  group (blank box),  $P_{LIP2}$  (diagonally shaded box),  $P_{LIPS}$  group (dotted box),  $P_{STAT}$  group (mosaic box), and  $P_{DYN}$  group (vertically lined box). The boxes represent the interquartile range (25–75%), the horizontal line within the boxes represents the median, and whiskers represent 10–90% error bars. T0: at the beginning of OLV; T1: OLV 15 min; T2: OLV 30 min; T3: OLV 45 min; T4: OLV 60 min. OI, oxygenation index;  $P_{aO_2}$ , arterial oxygen partial pressure; PEEP, positive end-expiratory pressure;  $P_0$ , “zero PEEP” group, as the control group;  $P_{LIP2}$ , “PEEP set to 2 cmH<sub>2</sub>O above the pressure of LIP of P-V curve” group;  $P_{LIPS}$ , “PEEP titration according to LIP of P-V curve” group;  $P_{STAT}$ , “PEEP titration according to static compliance” group;  $P_{DYN}$ , “PEEP titration according to dynamic compliance” group; OLV, one-lung ventilation; LIP, lower inflection point; P-V, pressure-volume.

basal level. We considered the reason to be that the airway pressure increased suddenly and was not maintained at a sufficient degree to open adequate alveoli.

It is reported that the optimal PEEP should be the pressure value of optimal lung compliance (20). Thus, our study also involved another two PEEP titration groups ( $P_{STAT}$  and  $P_{DYN}$ ), in which PEEP was titrated according to static or dynamic compliance. Dynamic lung compliance was affected by the elasticity of lung tissue, airway resistance, and the change in internal chest pressure, while static lung compliance was affected by the elasticity of the lung tissue alone. We assumed that the PEEP titrating strategy according to dynamic lung compliance might regulate whole chest homeostasis, while the PEEP titrating strategy according to static lung compliance only regulated the lung volume. We also considered that PEEP titration procedures made the airway resistance gradually increase, which would not markedly decrease the venous return. Our study demonstrated that respiratory mechanics showed lower  $P_{plat}$ , lower driving pressure, and higher dynamic compliance in group  $P_{DYN}$ . Our results showed that although PEEP titrating strategy according to dynamic compliance can improve respiratory mechanics, it does not adequately improve arterial oxygenation, which seemed to be inconsistent with other studies (2-4,6). Besides this, we found no significant effects on dead space ratio and

intrapulmonary shunt. In the literature, the intrapulmonary shunt is an essential reason for hypoxemia in OLV during thoracic surgical operations (6). Particularly in the lateral position, it is the result of gravity, as well as the mismatching of ventilation and blood flow. The existence of dead space is associated with the intrapulmonary shunt. Besides, the alveolar recruitment maneuver during OLV may play a vital role in the improvements of oxygenation and lung mechanics (21-24).

In our study, MAP and HR showed statistically significant differences at some time points, but this has no clinical meaning because of all changes within the physiological range. Considering the changes related to surgical operations, the use of anesthetic drugs, anesthesia depth changes, individual differences, and other factors, we generally thought PEEP titrating strategies had no significant effects on hemodynamic measurements (25). We also found that PIP and  $P_{plat}$  values significantly increased after PEEP titration. One report suggested that PEEP would increase airway pressure and decrease airway resistance, and would not result in increased inflammatory mediators (13). Thus, we consider that increased airway pressure would not injure the lung tissues. Furthermore, driving pressure (defined as tidal volume divided by respiratory system compliance), significantly decreased after PEEP titration. Therefore, ventilation at the lowest driving

pressure and the highest respiratory system compliance has been recommended for thoracic surgery (14). During OLV, driving pressure can be reduced after individualized PEEP titration, which may be related to a reduced incidence of postoperative pulmonary complications.

### Study limitations

Our study has some limitations. First, our patients ranged from ASA I to II, whose lung function had not deteriorated severely. Further study is still needed to determine whether the PEEP titrating strategies according to dynamic lung compliance valuable to severe patients. Second,  $\text{FiO}_2$  was set to 100% during OLV and 60% during TLV. It is appropriate to keep the  $\text{FiO}_2$  at the lowest possible level and increase if necessary. The incidence of postoperative pulmonary complications was not recorded. Last, in our study, the intrapulmonary shunt was estimated and calculated from several equations, which may be less accurate than direct measurements (6).

### Conclusions

The PEEP titrating strategy according to dynamic compliance can improve respiratory mechanics, whereas it has no significant effects on oxygenation, dead space ratio, and intrapulmonary shunt, suggesting that it is better during OLV for thoracic surgery.

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### Footnote

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[org/10.21037/apm-19-441](http://dx.doi.org/10.21037/apm-19-441)). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of Shanghai General Hospital (No. 2016KY109) and registered at the [chictr.org.cn](http://chictr.org.cn) website (ChiCTR-OPC-16008292). All patients were provided written informed consent before participation.

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