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Individualized positive end-expiratory pressure (PEEP) during one-lung ventilation for prevention of postoperative pulmonary complications in patients undergoing thoracic surgery

A meta-analysis

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Abstract

Background: Positive end-expiratory pressure (PEEP) is an important part of the lung protection strategies for one-lung ventilation (OLV). However, a fixed PEEP value is not suitable for all patients. Our objective was to determine the prevention of individualized PEEP on postoperative complications in patients undergoing one-lung ventilation.

Method: We searched the PubMed, Embase, and Cochrane and performed a meta-analysis to compare the effect of individual PEEP vs fixed PEEP during single lung ventilation on postoperative pulmonary complications. Our primary outcome was the occurrence of postoperative pulmonary complications during follow-up. Secondary outcomes included the partial pressure of arterial oxygen and oxygenation index during one-lung ventilation.

Result: Eight studies examining 849 patients were included in this review. The rate of postoperative pulmonary complications was reduced in the individualized PEEP group with a risk ratio of 0.52 (95% CI:0.37–0.73; $P=.0001$). The partial pressure of arterial oxygen during the OLV in the individualized PEEP group was higher with a mean difference 34.20 mm Hg (95% CI: 8.92–59.48; $P=.0004$). Similarly, the individualized PEEP group had a higher oxygenation index, MD: 49.07mmHg, (95% CI: 27.21–70.92; $P<.0001$).

Conclusions: Individualized PEEP setting during one-lung ventilation in patients undergoing thoracic surgery was associated with fewer postoperative pulmonary complications and better perioperative oxygenation.

Abbreviations: ARDS = acute respiratory distress syndrome, CI = confidence interval, EIT = electrical impedance tomography, OLV = one-lung ventilation, PCV = pressure-controlled ventilation, PEEP = positive end-expiratory pressure, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trial, VCV = volume-controlled ventilation.

Keywords: lung-protective ventilation strategy, one-lung ventilation, positive end-expiratory pressure

1. Introduction

Postoperative pulmonary complications have a strong effect on the morbidity and mortality of patients who have suffered surgery.[1–3] In thoracic surgery, one-lung ventilation is prone to volutrauma, barotrauma, atelectrauma, and oxygen toxicity, which are important aspects of ventilator-induced lung injury.[4] Intraoperative lung-protective ventilation strategy has been recommended to reduce postoperative pulmonary complications.[5–8] The term "protective ventilation" was defined as the combination of low tidal volumes, positive end-expiratory pressure (PEEP), and recruitment maneuvers.[9,10] During mechanical ventilation, low tidal volumes are considered to reduce intrapulmonary strain and stress, while the recruitment maneuvers and PEEP are used to avoid atelectasis formation and to maintain blood oxygenation.[11] However, there is no verdict as to whether high or low levels of intraoperative PEEP are better to reduce postoperative pulmonary complications.

Several randomized controlled trials (RCTs) of intraoperative ventilation showed that reduced tidal volume combined with high levels of PEEP during intraoperative ventilation prevents postoperative pulmonary complications.[6,8,12] However, other

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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RCTs have shown no difference in the development of postoperative pulmonary complications after intraoperative ventilation with low tidal volumes with either high or low levels of PEEP.[13,14]

Previous evidence suggests that 1 fixed PEEP value is unlikely to be appropriate for all patients and that there is considerable variability in the requirements for PEEP due to individual characteristics such as chest wall dimensions and shape, abdominal content, lung weights, and pleural pressures.[15–21] Application of individualized optimal PEEP intraoperatively not only reduces driving pressure and improves respiratory compliance and oxygenation but also reduces the incidence and severity of postoperative atelectasis.[22–25] It has not been reported for thoracic anesthesia where isolated, inflated lungs may be especially at risk. Therefore, we conducted a meta-analysis of RCTs to investigate the effect of individualized PEEP on one-lung ventilation during thoracic surgery.

2. Method

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. This investigation was conducted following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" statement recommended process.[26] The protocol was registered on PROSPERO. The electronic databases PubMed, Embase, Cochrane were searched until May, 2020, and the following words were searched as keywords (individualized

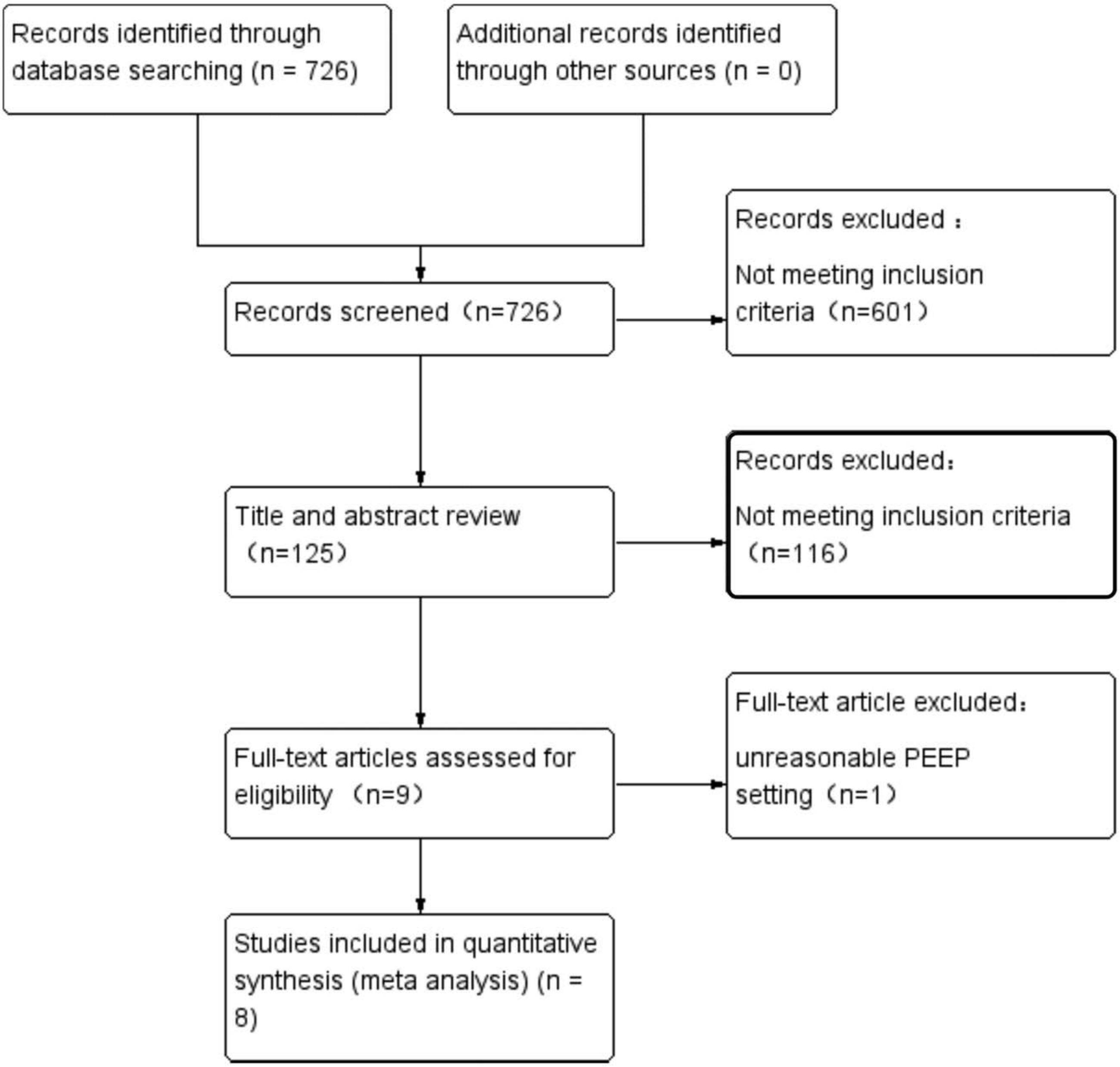

Figure 1. PRISMA flow diagram showing literature search results. Eight randomized controlled trials were included in the analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

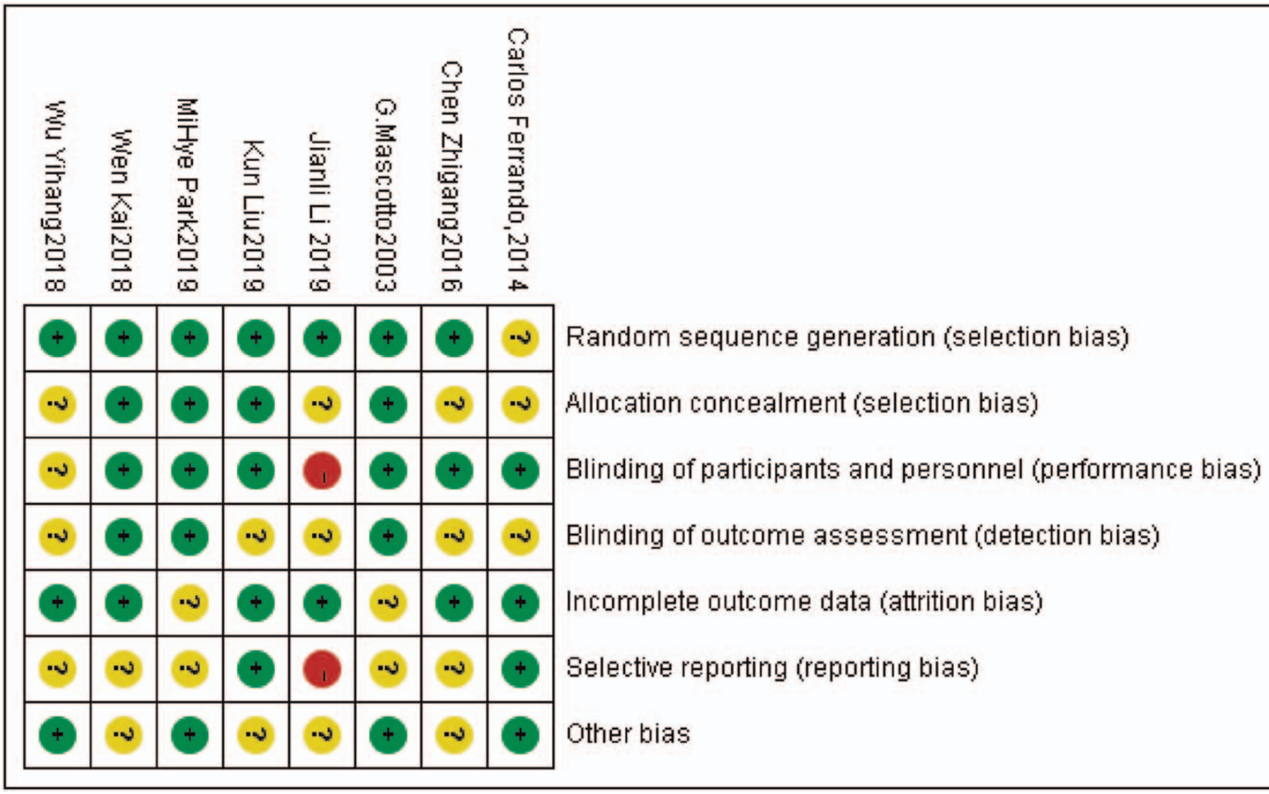

Figure 2. Risk of bias summary of included trials: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear.

positive end-expiratory pressure OR individualized PEEP OR individual positive end-expiratory pressure OR individual PEEP OR personalized PEEP) AND (one-lung ventilation OR single lung ventilation OR Thoracic surgery). The results of this search strategy were limited to RCTs and humans, we excluded case reports and observational studies. No language limits were placed on the search. We screened all articles after excluding duplicates and checked the reference lists of selected articles for other relevant studies.

The Cochrane Collaboration's Risk of Bias Tool for RCTs was employed to assess the methodological quality of each randomized trial, considering the following possible sources of bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other bias. The 2 participants independently assessed the risk of bias for the selected articles.

The primary outcome was the occurrence of postoperative pulmonary complications during follow-up. The secondary outcome was the PaO_2 and oxygenation index during one-lung ventilation. We use the Review Manager software (RevMan version 5.4) to conduct the meta-analyses. The coefficient I^2 was calculated to evaluate heterogeneity, with predetermined thresholds defined for low (25%–49%), moderate (50%–74%), and high (>75%) levels. In cases of moderate or high heterogeneity, a random-effects model was applied; otherwise, a fixed-effect model was employed. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study in turn for the meta-analysis. Publication bias is not evaluated because of the limited number (<10) of included studies.

For dichotomous outcomes, we calculated risk ratios (RR) with 95%CI, and for continuous outcomes, we used the mean difference (MD). When the continuous outcome was reported in some studies as median, range, and interquartile range, we estimated means and standard deviations using the method described by Weir et al.[27] For all analyses, *P* values less than .05 were considered significant.

3. Results

In our initial electronic search, we identified 726 potential articles. No additional studies were detected through manual scrutiny of reference lists of studies. After removal of duplicates, non-RCTs, and non-full texts, we screened 125 articles by title and abstract for eligibility. From these studies, we only included 8 trials for full-text evaluation.[22,28–34] We excluded 1 cross-over trial due to an unreasonable PEEP setting[35] (Fig. 1). A total number of 849 participants were included in the 8 studies. All participants were adult patients with American Society of Anesthesiologists physical status I–III. Application of the Cochrane Collaboration Risk of Bias tool (Fig. 2) suggested that the majority of trials had a low risk of bias. Publication bias was not assessed because the number of included studies was insufficient to explore a funnel plot or use more advanced regression-based assessments appropriately.

Table 1 presents the trial characteristics. Seven trials[22,28,29,31–34] PEEP fixed at 5 cm H_2O in their control group, 1 trial[30] set

Table 1

The characteristics of the included studies.

Reference	Population (n)	Surgery	Control group	Study group	Outcomes
Park et al (2019)	Control: n=145 individualized PEEP: n=147	Elective pulmonary resection or esophagectomy	Protective ventilation group: PEEP 5 cm H_2O	The driving pressure group: individualized PEEP	Postoperative complication, pneumonia or ARDS, in-hospital deaths, durations of intensive care unit stay, hospital stay, cerebral ischemic events, atrial fibrillation
Ferrando et al (2014)	Control: n=15 individualized PEEP: n=15	Elective lung resection	Control group: PEEP 5 cm H_2O	Study group: individualized PEEP	Dynamic compliance, oxygenation during OLV, airway resistance, cardiac index
Liu et al (2019)	$PEEP_5$ group: n=50 $PEEP_{EIT}$ group: n=50	Pneumonectomy, wedge resection, lobectomy, wedge+lobectomy	Control group: PEEP 5 cm H_2O	Study group: individualized PEEP by EIT	pH, PCO_2, PaO_2/FiO_2, Cdyn, P_{peak}, P_{mean}, and P_{plat} during OLV, use of vasoactive drugs, lung complications, duration of hospitalization
Mascott et al (2003)	Control: n=22 individualized PEEP: n=28	Pneumonectomy, lobectomy, atypical lung resection	Control group: receive zero PEEP	Study group: individualized PEEP on the best thoracopulmonary compliance	Lung chest wall compliance, PaO_2/FiO_2, hypoxic events during OLV, postanesthesia care unit discharge
Wu (2018)	Control: n=28 individualized PEEP: n=28	Thoracoscopic lobectomy	control group: PEEP 5 cm H_2O	Study group: individualized PEEP on the maximal static pulmonary compliance	Static pulmonary compliance, PaO_2/FiO_2 during OLV, Length of stay days of indwelling drainage tube, postoperative pulmonary complications
Chen (2016)	Control: n=39 individualized PEEP: n=39	Video-assisted right pulmonary lobectomy	Control group: PEEP 5 cm H_2O	Study group: individualized PEEP	Dynamic compliance, arterial blood gas analysis during OLV
Wen (2018)	Control: n=33 individualized PEEP: n=34	Elective lobectomy	General lung protective ventilation group (P group): PEEP 5 cm H_2O	Pulmonary ultrasound (L group): individualized PEEP by lung ultrasonography	Intraoperative hypoxic events, PaO_2/FiO_2 value during OLV, postoperative pulmonary complications, postoperative pain scores, cough, sputum, hospital stay
Li et al (2020)	PCV+OLA group: n=45 PCV group: n=44 VCV+OLA group: n=45 VCV group: n=42	Lobectomy wedge resection segmentectomy	PCV group: PEEP 5 cm H_2O VCV group: PEEP 5 cm H_2O	PCV+OLA group: PEEP produce the greatest dynamic compliance (Cdyn) VCV+OLA group: PEEP produce the greatest Cdyn	$PaCO_2$, pH, PaO_2/FiO_2, plasma concentration of neutrophil elastase, postoperative pneumonia, atelectasis, acute respiratory failure, duration of intensive care unit stay, duration of hospital stay

EIT=electrical impedance tomography, OLA=open-lung approach, OLV=one-lung ventilation, PCV=pressure-controlled ventilation, PEEP=positive end-expiratory pressure, VCV=volume-controlled ventilation.

zero PEEP as the control group. One trial[29] determined the individualized PEEP by electrical impedance tomography, 1 trial[31] by Pulmonary ultrasound, and 5 trials[22,30,32–34] determined PEEP by thoracopulmonary compliance measured. One[28] trial set the individualized PEEP to produce the lowest driving pressure. Regarding the ventilation patterns during one-lung ventilation, patients in 6 trials[28–33] underwent volume-controlled ventilation (VCV), while patients in 1 trial[22]

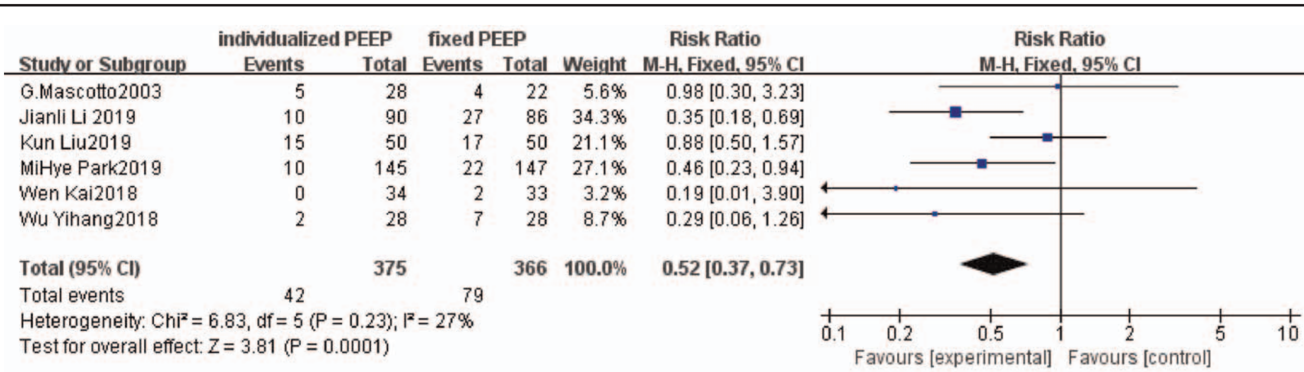

Figure 3. Forest plot of pooled data for the number of patients with postoperative pulmonary complications. CI=confidence interval.

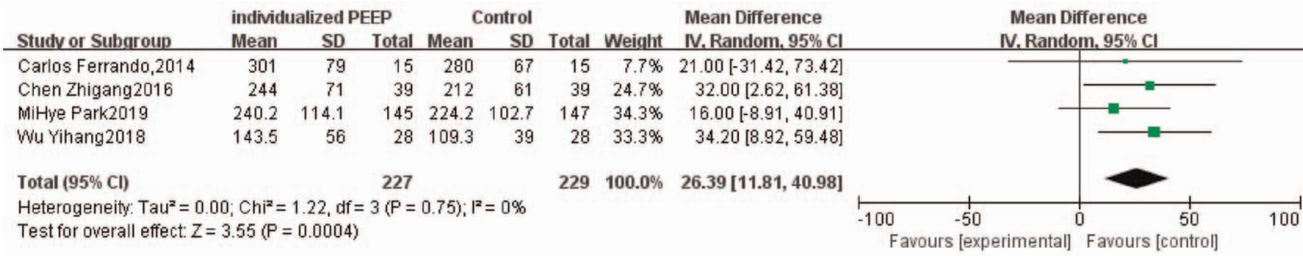

Figure 4. Forest plot of PaO_2 during one-lung ventilation. CI = confidence interval.

experienced pressure-controlled ventilation (PCV), and in 1 study[34] PCV and VCV are reported and compared.

Six studies[28–32,34] reported postoperative pulmonary complications. However, in 1 study, only postoperative radiological examination suggested atelectasis.[30] All reported postoperative pulmonary complications were followed up during the hospital stay. Two trials[28,34] reported the occurrence of postoperative acute respiratory distress syndrome (ARDS), in which the total number of patients who developed pneumonia or ARDS within a postoperative day were included in our analysis. Fixed effect models were chosen to reflect the heterogeneity of settings, interventions, and patient populations of the included studies. The number of patients with postoperative pulmonary complications was 42/375 (11.2%) in the individualized PEEP group and 79/366 (21.6%) in the control group, risk ratio: 0.52 (95% CI: 0.37–0.73; $P = .0001$) (Fig. 3).

Oxygenation during OLV was reported in 4 trials.[22,28,32,33] In regard to the time points, 1 trial[28] measured PaO_2 15 minutes after the PEEP setting during one-lung ventilation, 1 trial[22] measured 20 minutes after PEEP setting, 1[32] measured 30 min after PEEP setting, and 1[33] after 60 minutes. Although the time points of measurement were different, no significant heterogeneity was detected in the results (Fig. 4). The MD in PaO_2 during the OLV between the individualized PEEP group and control groups was 34.20 mm Hg, (95% CI: 8.92–59.48; $P = .0004$).

Five studies[29–32,34] reported the oxygenation index (PaO_2/FiO_2) during one-lung ventilation, 1[30] of which was reported graphically but did not specify what the error bars represented, and for this reason, we excluded this study from our meta-analysis. One study[34] reported the PaO_2/FiO_2 in different ventilation patterns (VCV or PCV), we incorporated the results into the analysis separately, In all included studies, PaO_2/FiO_2 decreased in both groups during OLV compared with DLV. Our analysis of PaO_2/FiO_2 during OLV resulted in a higher level in the individualized PEEP group compared with the control group (MD: 49.07 mmHg; 95% CI: 27.21–70.92; $P < .0001$) (Fig. 5). However, we detected a moderate degree of heterogeneity between the studies ($I^2 = 57\%$). To further explore potential causes of this high heterogeneity, we performed a sensitivity analysis by omitting 1 study from our pooled data synthesis.[31] The results of this analysis demonstrated that setting an individualized PEEP during one-lung ventilation leads to higher oxygenation index compared with setting a fixed PEEP with reduced heterogeneity, the MD (95%CI) being 37.72 (22.53–52.9) mmHg, $I^2 = 13\%$, $P < .00001$.

4. Discussion

This meta-analysis investigated the effect of individualized PEEP, compared with constant PEEP during one-lung ventilation on postoperative pulmonary complications. The setting of individualized PEEP during one-lung ventilation is of positive significance for reducing postoperative pulmonary complications. Although the included studies had different ventilation patterns (VCV or PCV) during one-lung ventilation, the resulting heterogeneity was minimal.

There are several types of PEEP titration methods to determine the individual PEEP, such as static or dynamic pulmonary compliance directed methods, electrical impedance tomography, esophageal manometry, and transpulmonary pressure directed PEEP titration procedures.[36] The optimum PEEP is the PEEP level that results in the greatest respiratory system compliance.[37,38] In the absence of previous lung injury, mechanical ventilation can destroy the fragile intercellular matrix structure of the lung.[39] General and local ischemia-reperfusion induced by hypotension, and hypoperfusion, surgical intervention, intraoperative blood loss, as well as tissue trauma itself, might lead to the release of inflammatory mediators and spread of bacteria that can

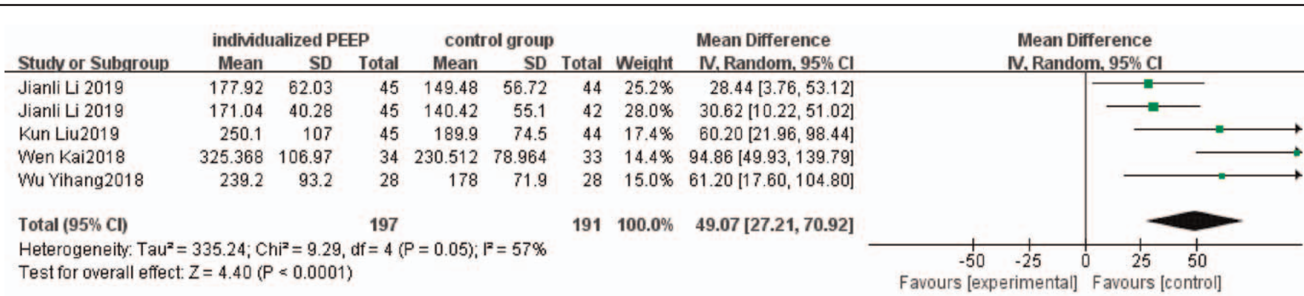

Figure 5. Oxygenation index (PaO_2/FiO_2) during one-lung ventilation. CI = confidence interval.

prime the lungs further to the stress of mechanical ventilation.[40] Titrating PEEP to achieve individual optimal levels has a strong pathophysiological rationale with potential benefits.[37] Individualized PEEP may potentially prevent alveolar collapse in the dependent lung in the lateral posture, increase the residual volume, improve the ventilation/perfusion ratio, reduce the shear damage caused by periodic opening and closing of the alveoli.[29] Patients with thoracic surgery often have a potential difference in their respiratory compliance because of mass size or site or frequently accompanying lung disease.[28] For these reasons, fixed-setting PEEP may lead to over-distend lungs or under-ventilated lungs.[28] In addition, the use of 100% FiO_2 is the first rescue therapy in the presence of hypoxemia. In this case, the use of an individualized level of PEEP would prevent reabsorptive atelectasis more than a standardized level of PEEP.[22]

The PaO_2 and PaO_2/FiO_2 during OLV were higher in the individualized PEEP group than the control group. Although the PaO_2 in the study group was higher than that in the control group, due to the management of intraoperative ventilation, PaO_2 in the 2 groups was not lower than normal. These promising results were still clinically advantageous. A change in PaO_2/FiO_2 ratios has been shown to represent a much more sensitive endpoint for ventilatory settings.[35] However, both criteria provide information on oxygenation reduction, and within safe ranges. The main mechanism by which PEEP improves oxygenation is the reduction of the right-to-left pulmonary shunt by keeping the alveolar open.[41]

However, we detected a high degree of heterogeneity in the analysis of PaO_2/FiO_2 during OLV, the reason may be the difference in the time point of blood gas analysis. In 1 study,[31] blood gas analysis during one-lung ventilation was performed immediately after PEEP setting, while in other studies, PaO_2/FiO_2 calculations were performed 30 to 60 minutes after the start of one-lung ventilation.

Our study is substantially different from the previous analysis of individualized PEEP in several respects. We focused exclusively on non-critically ill patients with uninjured lungs undergoing short-term ventilation for surgery. Thus, our results extend knowledge about protective ventilation and the potential role of the individualized PEEP. The protective role of intraoperative PEEP has been a matter of intense debate. This should be confirmed in future RCTs, in which the benefits of intraoperative ventilation strategies aiming at individualized PEEP for one-lung ventilation are determined.

Our meta-analysis had several limitations. First, postoperative pulmonary complications included postoperative lung injury, atelectasis, pulmonary infection, or barotrauma. Since only 2 of the trials included in the analysis provided subgroup data, we did not conduct a subgroup analysis. Second, the agreement of definitions of postoperative pulmonary complications and time-frame of diagnosis was heterogeneous among the included studies. Third, in 1 study,[30] the postoperative radiological examination showed atelectasis, but the pulmonary complications were not followed up. We still include corresponding data, for a fair majority of studies suggests that postoperation atelectasis is harmful. It can last for several days after surgery, increasing pulmonary complications, impairing respiratory function, and ultimately delaying patient discharge.[25,42,43] Finally, our study neglected thoracic surgery in children, so further research is needed for pediatric patients.

In conclusion, in patients undergoing one-lung ventilation, individualized PEEP is associated with less postoperative pulmonary complications and better perioperative oxygenation. However, to confirm these findings, some large randomized clinical trials are necessary.

Author contributions

All authors conceived and designed the study. Pule Li and Xia Kang conducted the literature review. Pule Li and Xia Kang abstracted the data. Pule Li conducted the analysis and drafted the manuscript. All authors revised the manuscript for important intellectual content.

Conceptualization: Pule Li, Mengrong Miao.
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Formal analysis: Pule Li, Xia Kang, Mengrong Miao, Jiaqiang Zhang.
Investigation: Pule Li.
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Software: Pule Li.
Supervision: Jiaqiang Zhang.
Visualization: Pule Li.
Writing – original draft: Pule Li.
Writing – review & editing: Pule Li, Mengrong Miao, Jiaqiang Zhang.

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