Positive end-expiratory pressure and recruitment maneuvers during one-lung ventilation: A systematic review and meta-analysis

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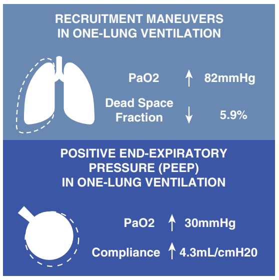
ABSTRACT

Background: It is unclear how positive end-expiratory pressure (PEEP) and recruitment maneuvers impact patients during one-lung ventilation (OLV). We conducted a systematic review and meta-analysis of the effect of lung recruitment and PEEP on ventilation and oxygenation during OLV.

Methods: A systematic review and random-effects meta-analysis were performed. Mean difference with standard deviation was calculated. Included studies were evaluated for quality and risk of bias using the Cochrane Risk of Bias tool and the modified Newcastle-Ottawa Score where appropriate.

Results: In total, 926 articles were identified, of which 16 were included in meta-analysis. Recruitment maneuvers increased arterial oxygen tension (PaO_2) by 82 mm Hg [20, 144 mm Hg] and reduced dead-space by 5.9% [3.8, 8.0%]. PEEP increased PaO_2 by 30.3 mm Hg [11.9, 48.6 mm Hg]. Subgroup analysis showed a significant increase in PaO_2 ($P = .0003$; +35.4 mm Hg [16.2, 54.5 mm Hg]) with PEEP compared with no PEEP but no such difference in comparisons with PEEP-treated controls. No significant difference in PaO_2 was observed between ``high" and ``low" PEEP-treated subgroups ($P = .29$). No significant improvement in PaO_2 was observed for subgroups coadministered PEEP, lung recruitment, and low tidal volumes. PEEP was associated with a modest but statistically significant increase in compliance ($P = .03$; 4.33 mL/cmH_2O [0.33, 8.32]). High risk of bias was identified in the majority of studies. Considerable heterogeneity was observed.

Conclusions: Recruitment maneuvers and PEEP have physiologic advantages during OLV. The optimal use of PEEP is yet to be determined. The evidence is limited by heavy use of surrogate outcomes. Future studies with clinical outcomes are necessary to determine the impact of recruitment maneuvers and PEEP during OLV. (J Thorac Cardiovasc Surg 2020;160:1112-22)



Meta-analysis of recruitment maneuvers and PEEP in one-lung ventilation.

CENTRAL MESSAGE

Recruitment maneuvers and PEEP have physiologic advantages during one-lung ventilation with yet-unclear clinical outcomes.

PERSPECTIVE

Lung-protective ventilation is poorly defined in one-lung ventilation for thoracic surgery. Our meta-analysis demonstrates physiologic improvements with lung recruitment and PEEP intraoperatively but a dearth of studies with clinical outcomes. This article should cautiously inform one-lung ventilation practices and encourage further research with patient-important outcomes.

See Commentaries on pages 1123 and 1124.

Intraoperative mechanical ventilation may cause lung injury in up to 33% of patients undergoing major surgery, with consequent increases in the risk of in-hospital, 7-day, and 30-day mortality.[1-6] This injury occurs through multiple mechanisms: alveolar overdistention with high tidal volume (TV) ventilation (volutrauma) and high airway pressures (barotrauma); alveolar collapse and reopening (atelectotrauma); and systemic inflammation caused by alveolar trauma and high inspired oxygen content (biotrauma).[6-10] Lung-protective ventilation encompasses mechanical-ventilation techniques—namely

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Abbreviations and Acronyms

- ARDS = acute respiratory distress syndrome
- OLV = one-lung ventilation
- PaO_2 = arterial oxygen tension
- PEEP = positive end-expiratory pressure
- RCT = randomized controlled trial
- TV = tidal volume
- Vd/Vt = dead-space fraction

low TV, application of positive end-expiratory pressure (PEEP), and recruitment maneuvers—intended to minimize these physiologic mechanisms of lung injury. Initial evidence for PEEP and recruitment maneuvers comes from acute respiratory distress syndrome (ARDS) literature.[11-14] Recent work has studied the translation of these critical care practices to elective surgical populations, with inconsistent results.[15-17] It has not been well established whether these maneuvers improve outcomes when applied during one-lung ventilation (OLV); thus, lung-protective ventilation is poorly defined for OLV for thoracic surgery.

Patients undergoing thoracic surgery represent a unique population with physiologic and clinical circumstances that complicate the application of conventional lung-protective ventilation techniques.[18,19] A proposed multi-hit model considers the unique challenges of OLV: (1) these patients often have baseline lung disease; (2) the deleterious effects of mechanical ventilation are exerted on a single lung tasked with the patient's entire respiratory load; (3) surgical manipulation of the nondependent lung may result in direct injury; (4) obligate collapse and re-expansion of the nondependent lung represents widespread atelectotrauma and is related to systemic inflammatory cascades.[7,8,20,21] Due to the positioning for most thoracic surgery (ie, lateral decubitus position), chest wall compliance is reduced and the ventilated lung is vulnerable to atelectotrauma as it experiences the weight of the mediastinum and abdomen.[8,21]

Furthermore, a paucity of evidence may explain the significant variation documented in lung-protective ventilation definition and implementation for OLV among anesthesiologists.[22-24] Most primary studies include small sample sizes and primarily report physiologic, rather than clinical, outcomes. Existing reviews of the literature have not conducted sufficiently broad searches to capture the breadth and depth of evidence regarding lung-protective ventilation during OLV as well as the multiple competing demands and interventions contained therein.[25,26] A comprehensive systematic review and meta-analysis is required to synthesize the available evidence with these limitations in mind. We conducted a systematic review and meta-analysis to determine how oxygenation and ventilation are affected by recruitment maneuvers and PEEP to the dependent lung during OLV for thoracic surgery in adults.

METHODS

Search Strategy and Selection Criteria

We performed a multistep systematic review process in which a preliminary scoping review was performed with intentionally broad inclusion criteria, followed by a more selective review focused on our ultimate research questions. The initial scoping review employed a structured methodology aimed at mapping the literature available, identifying gaps in the literature, and determining where systematic review would be valuable.[27,28] A MEDLINE search was conducted March 28, 2018, and repeated July 28, 2019, with the following search terms: "Respiration, Artificial/or lung-protective ventilation.mp. or exp Positive-Pressure Respiration" and "Thoracic Surgical Procedures/or one-lung ventilation.mp. or exp One-Lung Ventilation/or exp Anesthesia/." The search was not limited to articles published in English. A priori inclusion criteria were the following: (1) randomized controlled trials (RCT) and observational studies; (2) adults receiving OLV during thoracic surgery; and (3) comparison of intraoperative ventilation/anesthetic protocols. Studies involving cardiopulmonary bypass, lung transplantation, or those comparing lung deflation and airway devices were excluded. Gray literature searching was performed as well as manual searching of reference lists of reviewed studies. The results of this scoping review were categorized by 2 reviewers (J.K.P. and B.K.): included studies were grouped according to the lung-protective strategy evaluated and then analyzed to identify which outcome measures were repeated across studies. From this scoping review process, specific questions for systematic review and meta-analysis were developed and executed. We chose PEEP and lung recruitment for the subject of this meta-analysis.

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Screening, Data Abstraction, and Quality Assessment

A calibration exercise was performed with independent, duplicate review of 25 titles and abstracts by 2 reviewers (J.K.P. and B.K.). Due to complete agreement between reviewers, the remainder of the title and abstract screening was performed by a single reviewer (J.K.P.). Following a similar calibration exercise with complete agreement in duplicate full-text review by 2 reviewers (J.K.P. and B.K.), a single reviewer (J.K.P.) performed full-text review and data abstraction of study design, anesthetic protocol, and outcomes for each paper using a standardized form. A separate reviewer (B.K.) performed a check on all included studies to ensure agreement with data abstraction and risk of bias assessment. Graphical data were extracted using WebPlotDigitizer tool.[27,28] Data presented as median $\pm$ range were converted to mean $\pm$ standard deviation.[29] Included RCTs were evaluated using the Cochrane Risk of Bias tool; observational studies were evaluated using the modified Newcastle-Ottawa Score.[30-32]

Statistical Analysis

Meta-analysis was performed using RevMan (ver5.3) (Cochrane). Primary outcomes for meta-analysis of recruitment maneuvers were arterial oxygen tension (PaO_2), dead-space fraction (Vd/Vt); outcomes for meta-analysis of PEEP were PaO_2 and compliance. Mean difference with standard deviation was calculated. Random effects modeling was chosen a priori because of the expected between-study variation in sample population and effect size.[33] Heterogeneity was quantified using I^2 statistic. For the purpose of meta-analysis, when multiple independent comparisons existed in the same study, each unique comparison was treated as a unique study.[34] Sensitivity analysis was performed by excluding each study one at a time and repeating analysis to determine the robustness of the aggregated results.

In studies of PEEP, a priori subgroup analysis was planned to determine whether the use of low levels of PEEP in control groups (instead of NO PEEP) exerted a significant subgroup effect.

RESULTS

Figure 1 shows the PRISMA flow diagram including the studies identified at the scoping review stage as well as the meta-analysis stage. One-hundred seventeen studies were identified by our search at the scoping review stage; studies with similar comparisons were grouped into 7 categories (PEEP, recruitment maneuvers, TV, nondependent lung ventilation, ventilator mode, breath timing, and anesthetic choice). Clinical measurements were the primary outcome in only 1 study, with the remaining 116 primarily reporting physiologic outcomes. These data informed what questions were possible for meta-analysis and suggest that future meta-analysis could be performed for studies comparing tidal volume during OLV, non-dependent lung ventilation, and breath-timing.

Sixteen studies were included for qualitative/quantitative synthesis,[35-50] of which 11 were RCTs. Multiple comparisons existed in 5 studies: Abe and colleagues[47] evaluated 2 different anesthetic agents (sevoflurane, isoflurane), each with 2 levels of PEEP (4 and 8 cmH_2O); Ren and colleagues,[43] Hoftman and colleagues,[50] and Spadaro and colleagues[35] evaluated 2 levels of PEEP (5 and 10 cmH_2O); Leong and colleagues[44] used 3 values for PEEP (5, 8, and 10 cmH_2O). Characteristics and risk of bias for each study are reported in Tables E1 and E2.

Figure 2 shows the effect of recruitment on PaO_2 measured after 15 to 30 minutes of OLV. A statistically significant increase in PaO_2 by 82 mm Hg [20, 144 mm Hg] was observed in patients treated with recruitment. Considerable heterogeneity was observed ($I^2 = 82\%$) and appears to be driven predominantly by 1 study.[36]

Three studies evaluated recruitment maneuver effect on Vd/Vt.[36,38,40] A significant reduction in Vd/Vt by 5.9% [3.8, 8.0%] was observed in patients who underwent intraoperative recruitment maneuvers, with no identifiable heterogeneity (Figure 3).

Only 2 studies reported clinical outcomes between PEEP-treated and control groups.[41,46] Mascotto and colleagues[46] reported no significant difference in postanesthetic care unit length of stay between PEEP-treated patients and a control group treated with NO PEEP (48 vs 45 minutes, $P = .6$). This study also demonstrated no difference in postoperative radiograph appearance between groups.[46] Park and colleagues[41] reported that patients treated with individualized PEEP had significantly lower rates of composite postoperative pulmonary complications (5.5% vs 12.2%, $P = .047$) and ARDS (0 vs 5 cases, $P = .025$). No difference was reported in postoperative pneumonia rates (10 vs 17 cases, $P = .157$).[41]

Figure 4 displays the mean difference in PaO_2 between PEEP-treated and control groups in these studies, including a priori subgroups comparing PEEP-treated groups with controls with NO PEEP. A significant mean increase in PaO_2 was observed with PEEP ($P = .001$; +30.3 mm Hg [11.9, 48.6 mm Hg]). Considerable heterogeneity was observed ($I^2 = 84\%$). Subgroup comparison of PEEP with NO PEEP showed a significant increase in PaO_2 ($P = .0003$; +35.4 mm Hg [16.2, 54.5 mm Hg]), whereas there was no significant increase in PaO_2 when comparing individualized PEEP treatment vs controls treated PEEP of 5 cmH_2O. Although the subgroup comparing PEEP-treated groups to controls treated with NO PEEP showed a significant improvement in PaO_2 with application of PEEP, there was still residual heterogeneity ($I^2 = 84\%$) likely driven by the studies of Choi and colleagues[36] and Hoftman and colleagues.[50]

A post-hoc subgroup analysis investigated the impact of "high" (8-10 cmH_2O) versus "low" (3-5 cmH_2O) PEEP in the intervention groups. Figure 5 demonstrates a significant improvement in PaO_2 with both "high" and "low" PEEP. Although it appears that "low" PEEP may be associated with greater improvements in PaO_2 (+39.3 mm Hg) than the high PEEP subgroup (+21.9 mm Hg), no significant difference in effect was observed between these subgroups ($P = .29$). Considerable heterogeneity ($I^2 = 84\%$) was observed, driven largely by the studies by Park and colleagues[41] and Hoftman and colleagues.[50]

Figure 6 demonstrates the effect of PEEP on PaO_2 with post-hoc subgroup comparison of studies employing recruitment maneuvers for all patients versus those that do not. No difference in PaO_2 is observed in the recruitment subgroup ($P = .74$; –7.9 mm Hg [–22.9, 7.0 mm Hg]). No heterogeneity was observed ($I^2 = 0\%$). In contrast, PEEP significantly improved oxygenation in the no-recruitment subgroup ($P < .00001$; +49.9 mm Hg [29.0, 70.8 mm Hg]). Considerable heterogeneity ($I^2 = 84\%$) was observed. A significant subgroup effect is observed ($P = .0001$). Notably, the no-recruitment subgroup includes only studies using "high" TV (>7 mL/kg), and the recruitment subgroup only includes studies using "low" TV (<7 mL/kg). As such, these subgroup differences may be due either to the effect of TV or lung recruitment.

Figure 7 demonstrates that the addition of PEEP during OLV significantly improved compliance by 4.33 mL/cmH_2O [0.33, 8.32] ($P = .03$). Considerable heterogeneity was observed ($I^2 = 92\%$) as was a significant subgroup effect ($P = .001$).

Sensitivity analysis was performed for each intervention and outcome measure (data not shown). Minimal change in the mean effect was observed with the removal of any single article for most comparisons. There was a change in the significance of the overall effect reported for the effect of

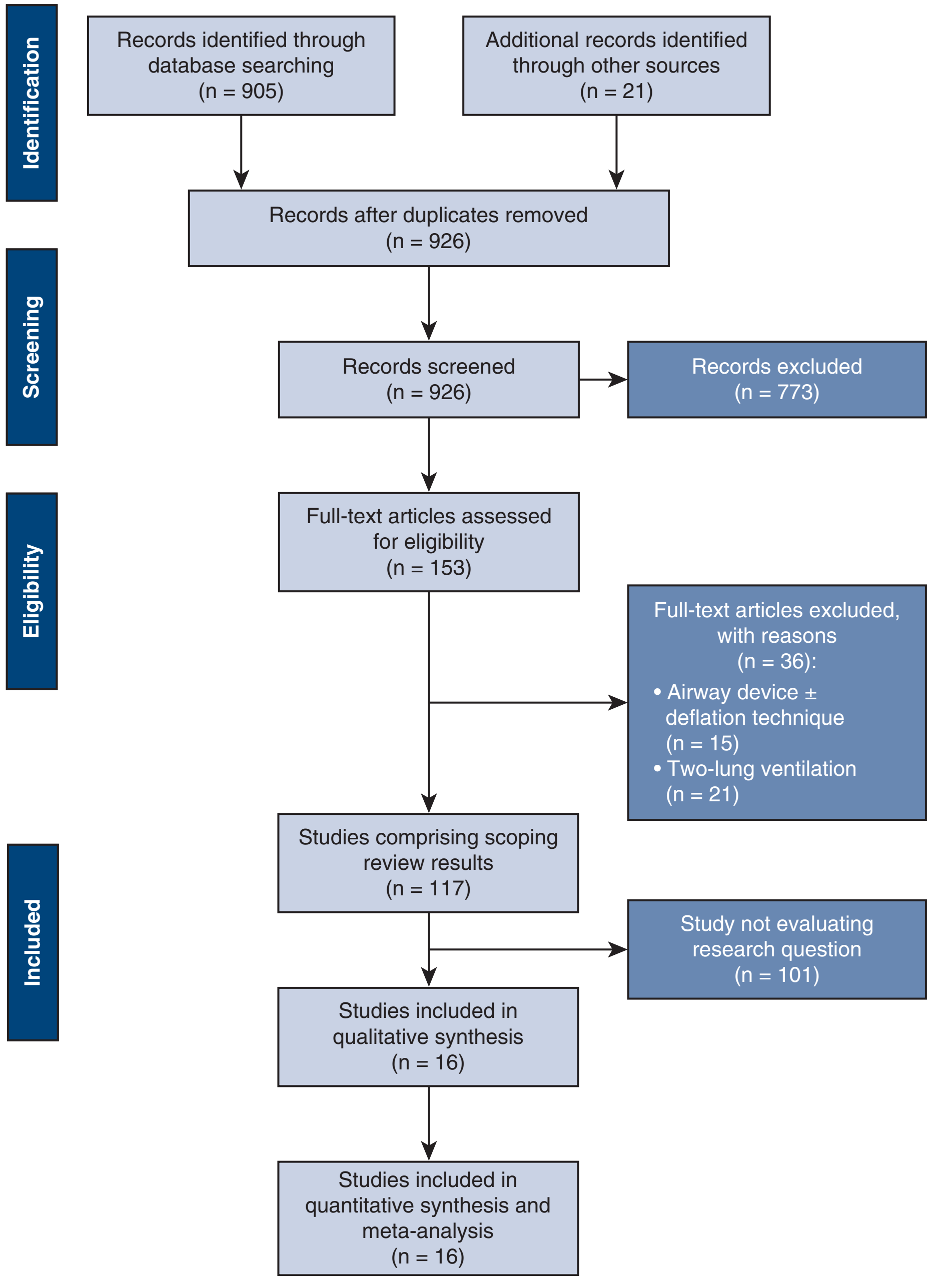

FIGURE 1. PRISMA flow diagram of the systematic study-selection process. We conducted a scoping review of lung-protective ventilation practices during OLV, followed by a systematic review and meta-analysis of the effect of lung recruitment and PEEP on ventilation and oxygenation during OLV for thoracic surgery in adults. The search strategy identified 905 articles from MedLine and EMBASE databases, with 21 additional articles identified through manual reference checks and other sources. Of these, 773 articles were unrelated to the research question and were excluded during title and abstract screen. A further 36 were excluded following full-text review: 21 did not involve one-lung ventilation and 15 studied airway devices. In total, 117 studies were produced by the scoping review, and were considered in the development of the meta-analysis. Systematic review of full-text articles was continued, and a further 101 articles that did not evaluate PEEP or recruitment maneuvers were excluded. The remaining 16 studies were included in qualitative and quantitative synthesis.

PEEP on compliance with the removal of the paper by Spadaro and colleagues.[35] The sensitivity of this finding to this one article indicates the statistically fragile —and clinically indeterminate—nature of this finding.

DISCUSSION

This systematic review and meta-analysis was performed to determine how oxygenation and ventilation are affected by recruitment maneuvers and PEEP to the dependent

Study or Subgroup	Recruitment Manoeuvre Mean [mmHg]	SD [mmHg]	Total	Control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
Choi 2015	258.2	84.6	33	255.8	83.6	33	23.0%	2.40 [−38.18, 42.98]
Park 2011	249	112.5	21	204	103.5	21	19.8%	45.00 [−20.38, 110.38]
Tusman 2002	470	76.8847	10	217	150.9736	10	14.7%	253.00 [147.99, 358.01]
Tusman 2004	244	84	12	144	73	12	20.2%	100.00 [37.03, 162.97]
Unzueta 2012	250.5	69	20	182.3	79.5	20	22.3%	68.20 [22.07, 114.33]
Total (95% CI)			**96**			**96**	**100.0%**	**82.11 [20.06, 144.17]**

Heterogeneity: $Tau^2 = 3938.91$; $Chi^2 = 22.48$, df = 4 ($P = .0002$); $I^2 = 82\%$
Test for overall effect: Z = 2.59 ($P = .010$)

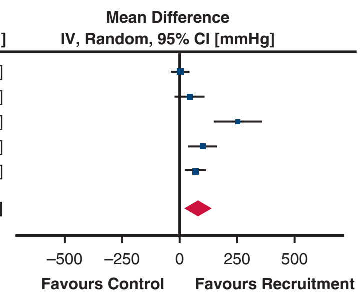

FIGURE 2. Forest plot of included studies evaluating the effect of recruitment maneuvers on PaO_2 after 30 minutes of OLV. The mean difference in PaO_2 between groups treated with a recruitment maneuver versus their study's respective control group is plotted, with a pooled mean estimate illustrated by the *diamond*. Recruitment was associated with a mean increase in PaO_2 by 82 mm Hg [20, 144 mm Hg], with considerable heterogeneity identified ($I^2 = 82\%$). *SD*, Standard deviation; *CI*, confidence interval.

lung during OLV for thoracic surgery in adults. The results demonstrate that both recruitment and PEEP significantly improve PaO_2 during OLV. In addition, this systematic review revealed that patient-important clinical measures of the effect of recruitment maneuvers and PEEP are lacking. A visual summary of the methods and key findings of this review are demonstrated in Figure 8.

The use of recruitment maneuvers was associated with significant improvements in PaO_2 during OLV, except for 2 studies, which found no significant difference in PaO_2 after 30 minutes of OLV.[36,37] One explanation for this may be that the timing of recruitment is important: Park and colleagues[36] and Choi and colleagues[37] both employed preemptive recruitment strategies before initiating OLV. Improvement in PaO_2 was observed when recruitment maneuvers were performed after the onset of OLV.[38-40] Our findings suggest that recruitment maneuvers performed during OLV improve PaO_2. Further, it appears that the heterogeneity is driven by differences in the timing of recruitment.

Stepwise recruitment maneuver was shown to decrease Vd/Vt during OLV. The 3 studies in this comparison all employed a similar procedure: stepwise increases in PEEP with fixed driving pressure of 20 cmH_2O (from 30/10 cmH_2O to 40/20 cmH_2O over 2 minutes).[36,38,40] A physiologic explanation has been proposed by Tusman and colleagues,[51] reporting that recruitment maneuvers redistribute inspired gas preferentially toward alveolar gas and that end-expiratory lung volume is increased by recruitment. As such, dead-space ventilation is minimized relative to tidal volume, thereby increasing alveolar surface area and reducing Vd/Vt.

No synergistic effect was observed with coadministration of PEEP and recruitment maneuvers. Most studies of lung recruitment in critical care literature combine recruitment with PEEP as an "open lung approach." In patients with ARDS, a recent meta-analysis demonstrated that recruitment maneuvers did not impact clinically important outcomes, although an earlier meta-analysis showed improved oxygenation and survival with the "open lung approach."[52,53] The difference between these 2 analyses is the inclusion of the landmark ART trial, which demonstrated increased mortality from an "open lung approach."[54,55] A qualitative review reported improvement in oxygenation following recruitment in thoracic surgery.[25] Liu and colleagues,[26] however, did not include lung recruitment in their meta-analysis of lung-protective ventilation for OLV. A mortality harm signal has been identified for lung recruitment during OLV for thoracic surgery.[10] These data suggest a nuanced effect of recruitment: immediate physiologic parameters may be improved by recruitment, but it may come at the expense of delayed lung inflammation/injury.

The physiologic rationale for PEEP includes the theoretical improvement in lung compliance by reducing the

Study or Subgroup	Recruitment Manoeuvre Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Choi 2015	20	6	33	24	8	33	36.6%	−4.00 [−7.41, −0.59]
Tusman 2004	53	4	12	60	5	12	32.5%	−7.00 [−10.62, −3.38]
Unzueta 2012	54	6	20	61	6	20	30.8%	−7.00 [−10.72, −3.28]
Total (95% CI)			**65**			**65**	**100.0%**	**−5.90 [−7.97, −3.84]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.88$, df = 2 ($P = .39$); $I^2 = 0\%$
Test for overall effect: Z = 5.60 ($P < .00001$)

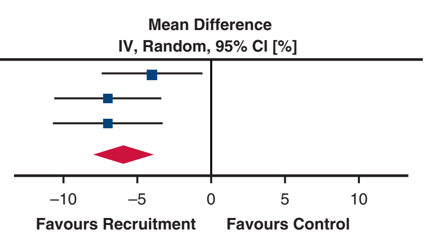

FIGURE 3. Forest plot of included studies evaluating the effect of recruitment maneuvers on Vd/Vt. Mean difference in Vd/Vt between groups treated with recruitment versus those without are plotted for each study, with a pooled estimate illustrated by the *diamond*. Recruitment was associated with a mean reduction in Vd/Vt of 5.9% [3.8, 8.0%], with no heterogeneity identified ($I^2 = 0\%$). *SD*, Standard deviation; *CI*, confidence interval.

Study or Subgroup	PEEP Mean [mmHg]	PEEP SD [mmHg]	PEEP Total	No PEEP Mean [mmHg]	No PEEP SD [mmHg]	No PEEP Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
12.1.1 Control groups with NO PEEP								
Abe 1998 [2] (ISO PEEP4)	190.6	22.9	10	131.1	11.8	10	9.7%	59.50 [43.53, 75.47]
Abe 1998 [2] (ISO PEEP8)	149	17.4	10	131.1	11.8	10	10.0%	17.90 [4.87, 30.93]
Abe 1998 [2] (SEV PEEP4)	192.4	26.9	10	127.2	14.3	10	9.4%	65.20 [46.32, 84.08]
Abe 1998 [2] (SEV PEEP8)	154.3	23.6	10	127.2	14.3	10	9.6%	27.10 [10.00, 44.20]
Choi 2015	240.5	68.4	33	255.8	83.6	33	7.4%	–15.30 [–52.15, 21.55]
Hoftman 2011 (PEEP 10)	146	78	41	149	80	41	7.7%	–3.00 [–37.20, 31.20]
Hoftman 2011 (PEEP 5)	144	76	41	149	80	41	7.7%	–5.00 [–38.78, 28.78]
Ren 2008 (PEEP 10)	292.1	90.6	10	140.5	54	10	4.5%	151.60 [86.23, 216.97]
Ren 2008 (PEEP 5)	294.6	148.6	10	140.5	54	10	2.6%	154.10 [56.11, 252.09]
Sentürk 2005	230.3	69.8	25	188.9	54.8	25	7.6%	41.40 [6.61, 76.19]
Valenza 2004	108	50	23	87.8	21.8	23	9.1%	20.20 [–2.09, 42.49]
Subtotal (95% CI)			**223**			**223**	**85.3%**	**35.36 [16.22, 54.50]**
Heterogeneity: Tau^2 = 761.15; Chi^2 = 63.08, df = 10 (*P* < .00001); I^2 = 84%								
Test for overall effect: Z = 3.62 (*P* = .0003)								
12.1.2 Control groups with PEEP 5cmH20								
Ferrando 2014	301	79	18	280	67	15	5.9%	21.00 [–28.82, 70.82]
Park 2019	224.2	102.7	147	240.2	114.1	145	8.8%	–16.00 [–40.91, 8.91]
Subtotal (95% CI)			**165**			**160**	**14.7%**	**–4.05 [–37.96, 29.87]**
Heterogeneity: Tau^2 = 280.74; Chi^2 = 1.70, df = 1 (*P* = .19); I^2 = 41%								
Test for overall effect: Z = 0.23 (*P* = .82)								
Total (95% CI)			**388**			**383**	**100.0%**	**30.25 [11.92, 48.58]**
Heterogeneity: Tau^2 = 834.24; Chi^2 = 77.22, df = 12 (*P* < .00001); I^2 = 84%								
Test for overall effect: Z = 3.23 (*P* = .001)								
Test for subgroup differences: Chi^2 = 3.93, df = 1 (*P* = .05), I^2 = 74.6%								

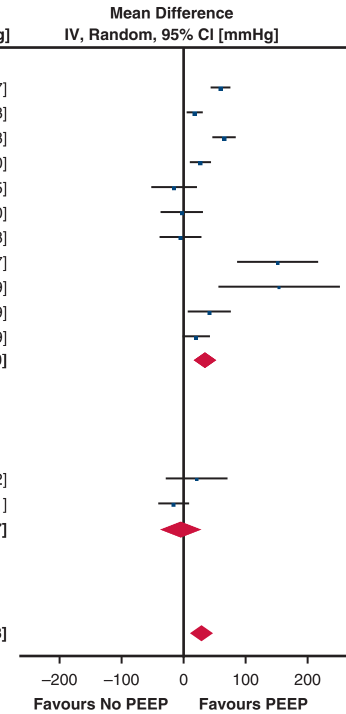

FIGURE 4. Forest plot of included studies evaluating PaO_2 in PEEP-treated and control groups, including a priori-defined subgroup comparison grouping studies with control groups treated with NO PEEP to studies with control groups treated with PEEP of 5 cmH_2O. The mean difference in PaO_2 is plotted for each study, with a pooled estimate illustrated by the *diamond*. When compared with controls treated with no PEEP, PEEP administration in the intervention group was associated with a mean increase in PaO_2 by 35.4 mm Hg [16.2, 54.5 mm Hg], with considerable heterogeneity ($I^2 = 84\%$). When compared with controls treated with PEEP of 5 cmH_2O, individualized PEEP administration in the intervention group had no significant impact on PaO_2 ($P = .19$; –4.1 [–37.9, 29.9 mm Hg]). *PEEP*, Positive end-expiratory pressure; *SD*, standard deviation; *CI*, confidence interval; *ISO*, isoflurane; *SEV*, sevoflurane.

proportion of collapsed alveoli.[36,45] Our meta-analysis result that PEEP significantly increases compliance is consistent with this theory. However, in sensitivity analysis the removal of the paper by Spadaro and colleagues eliminates the statistical significance. In addition, while 5 studies showed improvement in compliance with PEEP, 2 may have artificially enhanced the impact of PEEP on compliance: Ferrando and colleagues[42] employed a PEEP-titration protocol titrated to optimal compliance, so it is expected that their treatment group demonstrates improved compliance, and Valenza and colleagues[45] employed a protocol combining recruitment with PEEP. Furthermore, improvement in compliance was reported by 3 studies that employed ‘‘low’’ TV, whereas others in this comparison employed ‘‘high’’ TV.[35,36,42] It has been previously shown that coadministration of ‘‘high’’ TV and PEEP can worsen compliance[56]: the indeterminate result of this meta-analysis may in part be attributed to the interaction of ‘‘high’’ TV ventilation with PEEP to lower compliance. This lack of improvement may also be driven by heterogeneity in the reporting/measurement of compliance; all studies use different measures of compliance including dynamic,[36] static,[42] lung–chest wall,[46] effective,[45] and respiratory system[35] compliances.

Although it has been theorized that alveolar overdistension occurring from high PEEP may decrease perfusion of the dependent lung and worsen intrapulmonary shunt, this has not been demonstrated in studies using clinically relevant levels of PEEP.[35,57,58] Spadaro and colleagues[35] describes a significant decrease in shunt fraction and increase in respiratory system compliance with the addition of PEEP of 10 cmH_2O compared with no PEEP during OLV and similar improvements in shunt fraction with PEEP 5 cmH_2O during abdominal surgery.[58] The authors of these studies suggest that PEEP reduces shunt fraction by minimizing the atelectasis that typically occurs while under anesthesia.[35,58] Only one of the papers included in our review included shunt fraction among the physiologic outcome measures studied.[35]

The interplay between TV and PEEP cannot be ignored. Critical care literature has demonstrated that ‘‘low’’ TV improves patient outcomes.[4,13] Blank and colleagues[59] reported that ‘‘low’’ TV with adequate PEEP represents a lung protective ventilation strategy. In our meta-analysis,

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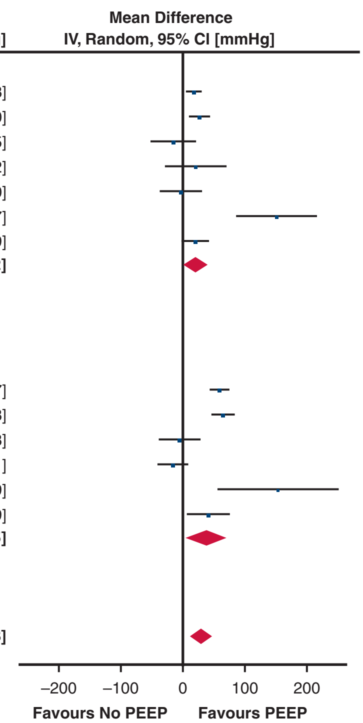
Study or Subgroup	PEEP Mean [mmHg]	PEEP SD [mmHg]	PEEP Total	No PEEP Mean [mmHg]	No PEEP SD [mmHg]	No PEEP Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
19.1.1 Intervention groups treated with "high" PEEP								
Abe 1998 [2] (ISO PEEP8)	149	17.4	10	131.1	11.8	10	10.0%	17.90 [4.87, 30.93]
Abe 1998 [2] (SEV PEEP8)	154.3	23.6	10	127.2	14.3	10	9.6%	27.10 [10.00, 44.20]
Choi 2015	240.5	68.4	33	255.8	83.6	33	7.4%	−15.30 [−52.15, 21.55]
Ferrando 2014	301	79	18	280	67	15	5.9%	21.00 [−28.82, 70.82]
Hoftman 2011 (PEEP 10)	146	78	41	149	80	41	7.7%	−3.00 [−37.20, 31.20]
Ren 2008 (PEEP 10)	292.1	90.6	10	140.5	54	10	4.5%	151.60 [86.23, 216.97]
Valenza 2004	108	50	23	87.8	21.8	23	9.1%	20.20 [−2.09, 42.49]
Subtotal (95% CI)			**145**			**142**	**54.1%**	**21.90 [2.58, 41.22]**
Heterogeneity: $Tau^2 = 417.71$; $Chi^2 = 21.59$, df = 6 ($P = .001$); $I^2 = 72\%$								
Test for overall effect: Z = 2.22 ($P = .03$)								
19.1.2 Intervention groups treated with "low" PEEP								
Abe 1998 [2] (ISO PEEP4)	190.6	22.9	10	131.1	11.8	10	9.7%	59.50 [43.53, 75.47]
Abe 1998 [2] (SEV PEEP4)	192.4	26.9	10	127.2	14.3	10	9.4%	65.20 [46.32, 84.08]
Hoftman 2011 (PEEP 5)	144	76	41	149	80	41	7.7%	−5.00 [−38.78, 28.78]
Park 2019 (1)	224.2	102.7	147	240.2	114.1	145	8.8%	−16.00 [−40.91, 8.91]
Ren 2008 (PEEP 5)	294.6	148.6	10	140.5	54	10	2.6%	154.10 [56.11, 252.09]
Sentürk 2005	230.3	69.8	25	188.9	54.8	25	7.6%	41.40 [6.61, 76.19]
Subtotal (95% CI)			**243**			**241**	**45.9%**	**39.25 [6.25, 72.25]**
Heterogeneity: $Tau^2 = 1350.34$; $Chi^2 = 43.67$, df = 5 ($P < .00001$); $I^2 = 89\%$								
Test for overall effect: Z = 2.33 ($P = .02$)								
Total (95% CI)			**388**			**383**	**100.0%**	**30.25 [11.92, 48.58]**
Heterogeneity: $Tau^2 = 834.24$; $Chi^2 = 77.22$, df = 12 ($P < .00001$); $I^2 = 84\%$								
Test for overall effect: Z = 3.23 ($P = .001$)								
Test for subgroup differences: $Chi^2 = 0.79$, df = 1 ($P = .37$), $I^2 = 0\%$								



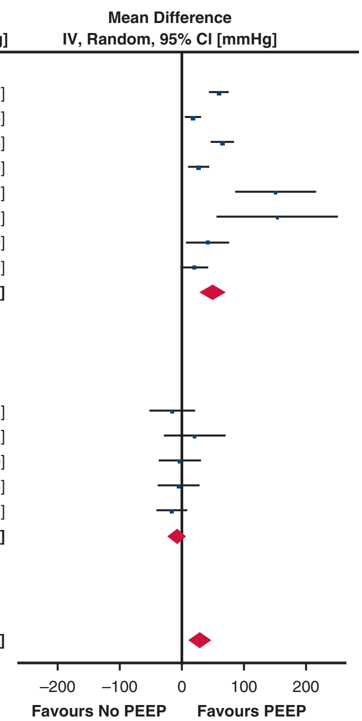
Footnotes
(1) Low PEEP group was experimental group with minimized driving pressures

FIGURE 5. Forest plot of included studies evaluating PaO_2 in PEEP-treated and control groups, with subgroup analysis comparing "high" (8-10 cmH_2O) and "low" (3-5 cmH_2O) PEEP treatment in the intervention groups. Mean difference in PaO_2 for each study is shown, and the overall mean estimate demonstrated by the *diamond*. The "high" PEEP subgroup demonstrated a mean improvement in PaO_2 by 21.9 mm Hg [2.6, 41.2 mm Hg] with substantial heterogeneity ($I^2 = 72\%$). The "low" PEEP subgroup demonstrated a mean increase in PaO_2 by 39.3 mm Hg [6.3, 72.3 mm Hg], with considerable heterogeneity ($I^2 = 89\%$). No difference between subgroups was observed ($P = .37$). *PEEP*, Positive end-expiratory pressure; *SD*, standard deviation; *CI*, confidence interval; *ISO*, isoflurane; *SEV*, sevoflurane.

no improvement in PaO_2 was observed, regardless of PEEP, in groups treated with "low" TV,[36,41,42] suggesting that the addition of PEEP does not change PaO_2 during "low" TV ventilation, unlike the effect of PEEP during greater TV ventilation. Given the strength of association between "low" TV ventilation and improved clinical outcomes, our finding that "high" TV with PEEP increases PaO_2 must be viewed circumspectly. If anything, it calls into question the practice of using PaO_2 as a surrogate predictor of clinical course. Future work regarding PEEP must employ the accepted practice of "low" TV ventilation, and should consider clinical outcomes rather than surrogates.

Although PEEP is employed in lung-protective ventilation strategies, its efficacy varies depending on the population studied. It may be that only certain patients respond to PEEP, perhaps relating to the amount of "recruitable alveoli."[12,45,50] Heterogeneity in the PEEP treatment effect has been demonstrated, with PEEP resulting in lower mortality and earlier unassisted breathing in patients with moderate to severe, but not mild, ARDS.[12] No consensus has been reached in any population studied as to whether "high" or "low" PEEP is preferable.[60] Consistent with this, although our meta-analysis suggested "low" PEEP was associated with greater improvement in PaO_2 than "high" PEEP, no significant difference between subgroups was observed. These data lend support to the growing body of evidence in support of individualized PEEP: no one "perfect" level of PEEP exists for all patients.[12,60] Four studies in our review considered individualized PEEP or attempted to identify characteristics of patients who might respond best to PEEP.[41,42,45,50] Valenza and colleagues[45] observed no overall PaO_2 improvement with PEEP during OLV; however, they reported a significant improvement in PaO_2 among the subset of patients with a "high" preoperative forced expiratory volume in 1 second, suggesting a subset of patients who may be "PEEP-Responders."[45] Hoftman and colleagues[50] failed to demonstrate an association between forced expiratory volume in 1 second or other preoperative factors and PEEP-responsiveness. Despite the hypothesis that patients declare themselves as either "PEEP-responders" or "PEEP non-responders," we found no difference in

Study or Subgroup	PEEP Mean [mmHg]	PEEP SD [mmHg]	PEEP Total	No PEEP Mean [mmHg]	No PEEP SD [mmHg]	No PEEP Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]
21.1.1 All patients treated with "High" Tidal Volume and NO Recruitment								
Abe 1998 [2] (ISO PEEP4)	190.6	22.9	10	131.1	11.8	10	9.7%	59.50 [43.53, 75.47]
Abe 1998 [2] (ISO PEEP8)	149	17.4	10	131.1	11.8	10	10.0%	17.90 [4.87, 30.93]
Abe 1998 [2] (SEV PEEP4)	192.4	26.9	10	127.2	14.3	10	9.4%	65.20 [46.32, 84.08]
Abe 1998 [2] (SEV PEEP8)	154.3	23.6	10	127.2	14.3	10	9.6%	27.10 [10.00, 44.20]
Ren 2008 (PEEP 10)	292.1	90.6	10	140.5	54	10	4.5%	151.60 [86.23, 216.97]
Ren 2008 (PEEP 5)	294.6	148.6	10	140.5	54	10	2.6%	154.10 [56.11, 252.09]
Sentürk 2005	230.3	69.8	25	188.9	54.8	25	7.6%	41.40 [6.61, 76.19]
Valenza 2004	108	50	23	87.8	21.8	23	9.1%	20.20 [–2.09, 42.49]
Subtotal (95% CI)			**108**			**108**	**62.5%**	**49.91 [29.02, 70.80]**
Heterogeneity: $Tau^2 = 646.50$; $Chi^2 = 45.09$, df = 7 ($P < .00001$); $I^2 = 84\%$								
Test for overall effect: Z = 4.68 ($P < .00001$)								
21.1.2 All patients treated with "Low" Tidal Volume and NO Recruitment								
Choi 2015	240.5	68.4	33	255.8	83.6	33	7.4%	–15.30 [–52.15, 21.55]
Ferrando 2014	301	79	18	280	67	15	5.9%	21.00 [–28.82, 70.82]
Hoftman 2011 (PEEP 10)	146	78	41	149	80	41	7.7%	–3.00 [–37.20, 31.20]
Hoftman 2011 (PEEP 5)	144	76	41	149	80	41	7.7%	–5.00 [–38.78, 28.78]
Park 2019 (1)	224.2	102.7	147	240.2	114.1	145	8.8%	–16.00 [–40.91, 8.91]
Subtotal (95% CI)			**280**			**275**	**37.5%**	**–7.93 [– 22.86, 7.01]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.96$, df = 4 ($P = .74$); $I^2 = 0\%$								
Test for overall effect: Z = 1.04 ($P = .30$)								
Total (95% CI)			**388**			**383**	**100.0%**	**30.25 [11.92, 48.58]**
Heterogeneity: $Tau^2 = 834.24$; $Chi^2 = 77.22$, df = 12 ($P < .00001$); $I^2 = 84\%$								
Test for overall effect: Z = 3.23 ($P = .001$)								
Test for subgroup differences: $Chi^2 = 19.49$, df = 1 ($P < .0001$), $I^2 = 94.9\%$								



Footnotes
(1) Low PEEP group was experimental group with minized driving pressures

FIGURE 6. Forest plot of studies comparing mean difference in PaO_2 from PEEP administration with subgroups comparing studies employing recruitment maneuvers and "low" (<7 mL/kg) TV for all patients versus studies employing "high" (>7 mL/kg) TV and NO recruitment maneuvers for any patients. The mean difference is plotted for each study, with pooled estimates illustrated by the *diamonds*. PEEP is associated with a significant increase in PaO_2 in the no-recruitment/"high"-TV subgroup ($P < .00001$; 49.9 mm Hg [29.0, 70.8 mm Hg]), but not in the recruitment/"low"-TV subgroup. A significant subgroup difference was observed ($P = .0001$). *PEEP*, Positive end-expiratory pressure; *SD*, standard deviation; *CI*, confidence interval; *ISO*, isoflurane; *SEV*, sevoflurane.

PaO_2 between protocols using personalized PEEP and protocols using standard PEEP.[41,42] It is unclear how the results may have changed had individualized PEEP been compared against controls with NO PEEP.

Thus, the true role of PEEP in lung-protective ventilation for OLV requires further elucidation. Recent interest in the "driving pressure" concept has suggested a more complex role for PEEP. Only 1 study in our analysis titrated PEEP to optimal driving pressure, however, data from 2-lung ventilation in ARDS suggest that greater driving pressures are associated with in-hospital mortality.[41,61] Greater insight into the role of PEEP during OLV may be provided by the ongoing PROTHOR trial, among the first RCTs adequately powered to determine whether a difference in postoperative pulmonary complications exists between low and high PEEP-treated adults undergoing OLV for thoracic surgery.[62]

Limitations

A limitation of the source data is that it relies heavily on surrogate rather than patient-important outcomes. The few included studies that reported clinical outcomes did not find significant differences between their respective treatment and control groups. Since significant differences were reported between physiologic measures but not in clinical outcomes, the usefulness of physiologic measurements as surrogate outcomes may be questioned. Further, the preference for physiologic surrogate outcomes in the published literature may represent a publication bias that explains why so few published studies report clinical outcomes. Nearly all included studies were described as high risk of bias, mainly due to the absence of blinding. However, it may be practically unfeasible and unsafe for the anesthesiologist ventilating the patient to be blinded to their treatments. Given this structural challenge of perioperative research, the use of the conservative Cochrane risk of bias tool for the evaluation of included studies should not discourage the cautious interpretation of our meta-analysis, However, the overall low scores produced emphasize the need for greater quality research. A further limitation is that most included studies had small sample sizes. However, this reduces power to detect true differences

Study or Subgroup	PEEP Mean [mL/cmH20]	PEEP SD [mL/cmH20]	PEEP Total	No PEEP Mean [mL/cmH20]	No PEEP SD [mL/cmH20]	No PEEP Total	Weight	Mean Difference IV, Random, 95% CI [mL/cmH20]
12.3.1 Control groups with NO PEEP								
Choi 2015	26.8	6.5	33	20.3	5	33	11.1%	6.50 [3.70, 9.30]
Leong 2007 (PEEP10)	43.7	3.1	10	50.3	5	10	10.7%	−6.60 [−10.25, −2.95]
Leong 2007 (PEEP5)	51.6	3.6	11	50.3	5	10	10.6%	1.30 [−2.46, 5.06]
Leong 2007 (PEEP8)	43.9	3	11	50.3	5	10	10.7%	−6.40 [−9.97, −2.83]
Mascotto 2003	36.2	6.8	28	32.9	7.9	22	10.4%	3.30 [−0.85, 7.45]
Rauseo 2018	71.06	12.25	13	56.17	18.18	13	5.7%	14.89 [2.97, 26.81]
Spadaro 2018 (PEEP 10)	29.5	8	41	22	5	41	11.1%	7.50 [4.61, 10.39]
Spadaro 2018 (PEEP 5)	25.5	7	41	22	5	41	11.2%	3.50 [0.87, 6.13]
Valenza 2004	46.6	13	23	35.1	7	25	9.3%	11.50 [5.52, 17.48]
Subtotal (95% CI)			**211**			**205**	**90.8%**	**3.21 [−0.76, 7.18]**
Heterogeneity: Tau² = 31.28; Chi² = 80.95, df = 8 (*P* < .00001); I² = 90%								
Test for overall effect: Z = 1.58 (*P* = .11)								
12.3.2 Control groups with PEEP 5cmH20								
Ferrando 2014	50	11	18	35	7	15	9.2%	15.00 [8.81, 21.19]
Subtotal (95% CI)			**18**			**15**	**9.2%**	**15.00 [8.81, 21.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.75 (*P* < .00001)								
Total (95% CI)			**229**			**220**	**100.0%**	**4.33 [0.33, 8.32]**
Heterogeneity: Tau² = 35.39; Chi² = 95.45, df = 9 (*P* < .00001); I² = 91%								
Test for overall effect: Z = 2.12 (*P* = .03)								
Test for subgroup differences: Chi² = 9.87, df = 1 (*P* = .002), I² = 89.9%								

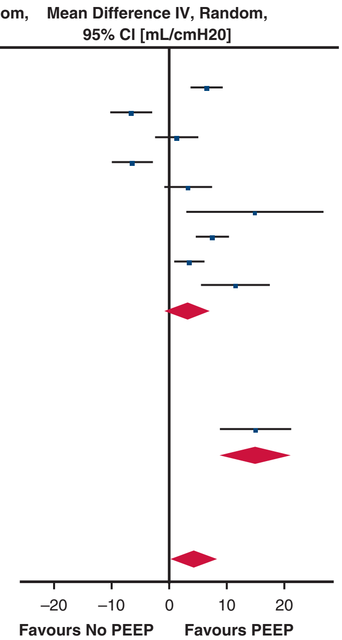


FIGURE 7. Forest plot comparing mean difference in compliance in PEEP-treated and control groups, including a priori subgroup comparison of control groups with no PEEP versus controls treated with PEEP of 5 cmH_2O. An overall statistically significant improvement in compliance was observed with the addition of PEEP, although considerable heterogeneity exists in this comparison ($P = .03$, 4.33 [95% confidence interval, 0.33-8.32]). *PEEP*, Positive end-expiratory pressure; *SD*, standard deviation; *CI*, confidence interval.

and thus does not invalidate our findings that recruitment maneuvers and PEEP are associated with improved PaO_2. In addition, for meta-analysis, we treated multiple comparisons in the same article as unique studies. While this is a methodologic practice that is promoted by the Cochrane Collaboration, the consequence is that this practice is likely to result in more conservative estimates of effect; by treating these subgroups as coming from different studies in the context of random effects modeling, the variance inflates and the chance of finding a null effect increases.[36]

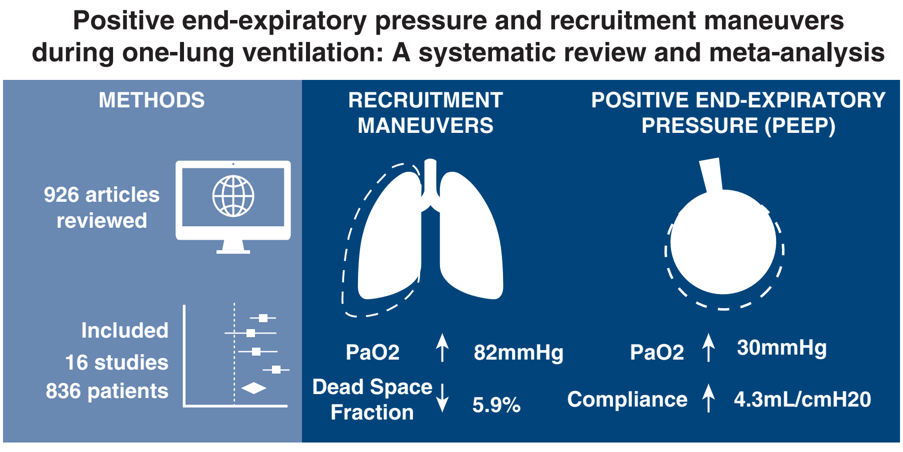


FIGURE 8. A systematic literature search of lung-protective ventilation strategies for one-lung ventilation identified 926 articles, of which 16 were selected for meta-analysis. Lung recruitment was evaluated in 5 studies, with significant improvements in PaO_2 by 82 mm Hg and significant reductions in Vd/Vt by 5.9%. PEEP was evaluated in 12 studies, finding a significant improvement in PaO_2 by 30 mm Hg. The evidence is unclear regarding the optimal selection of PEEP. Despite evidence of improvement in physiologic outcomes with recruitment and PEEP, clinical outcomes were notably absent in all included studies. This article should cautiously inform one-lung ventilation practices and encourage further research with patient-important outcomes. *PEEP*, Positive end-expiratory pressure.

Lastly, considerable heterogeneity exists for many of the comparisons in our meta-analysis. Clinical variation across anesthetic protocols is likely the biggest driver of heterogeneity.

CONCLUSIONS

This systematic review and meta-analysis assessed the existing evidence regarding lung-protective ventilation during OLV. Recruitment maneuvers and PEEP are associated with significant improvements in PaO_2 during OLV. Recruitment maneuvers were associated with reduced Vd/Vt. The optimal use of PEEP is yet to be determined, especially as emerging evidence suggests driving pressure may be an important parameter. Use of PEEP was not associated with improvements in compliance, although this finding may be due to a high degree of unresolved heterogeneity driven by a small number of studies using different definitions of compliance. Although these findings suggest that intraoperative lung recruitment appears to have physiologic advantages during OLV, the existing evidence is considerably limited due its use of predominantly surrogate outcomes. Future studies with patient-important clinical outcomes are needed to elucidate whether recruitment maneuvers and PEEP during OLV are truly lung-protective.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: one-lung ventilation, lung-protective ventilation, meta-analysis, positive end-expiratory pressure (PEEP), lung recruitment

TABLE E1. Characteristics of included studies

Article	Control intervention	Experimental intervention	FiO_2	PEEP cmH_2O	TV, mL/kg	Recruitment maneuver	Anesthetic	Thoracic epidural	Ventilator mode
Park et al, 2019[41]	PEEP 5 cmH_2O	Trial for the lowest driving pressure started at 5 min of OLV by increasing PEEP from 2 to 10 cm H_2O incrementally.	1		6	Y	Sevoflurane + remifentanil	Thoracic epidural	VCV
Rauseo et al, 2018[49]	NO PEEP	PEEP decrement from 20 by 2 until maximal respiratory system compliance achieved. Optimal compliance at PEEP 6 ± 0.8 cmH_2O (range 5-8 cmH_2O).		5-8	6-8	Y	Propofol TIVA + remifentanil		VCV
Choi et al, 2015[36]	No recruitment	PIP and PEEP were sequentially increased from 30/10 to 35/15 cmH_2O in steps of 5 breaths and then to 40/20 cmH_2O for 10 breaths with an I:E ratio of 1:1.	1	0	6	Y	Sevoflurane + remifentanil		PCV
Ferrando et al, 2014[42]	PEEP 5 cmH_2O	PEEP decrement from 20 by 2 until maximal dynamic compliance achieved. Optimal compliance at PEEP 10 after titration ±2.	1	5, 10	5-7	Y	Sevoflurane + remifentanil	Thoracic epidural	VCV
Unzueta et al, 2012[38]	No recruitment	PEEP was increased from 10 to 15 cmH_2O for 5 breaths and then to 20 cmH_2O. After reaching a PEEP of 20 cmH_2O, driving pressure was increased to 20 cmH_2O to reach a final PIP of 40 cmH_2O, and maintained for 10 breaths.	1	8	6	Y	Propofol TIVA	Paravertebral block	VCV
Hoftman et al, 2011[50]	No PEEP	PEEP 5, 10 cmH_2O	1	0, 5, 10	6	Y	Desflurane		VCV
Park et al, 2011[37]	No recruitment	PIP and PEEP of 40/0 cmH_2O for 10 breaths. Then PEEP of 15 cmH_2O was applied to both lungs during TLV. Recruitment maneuver stopped just before the start of OLV.	1	5	6	Y	Sevoflurane		
Ren et al, 2008[43]	PEEP 5 cmH_2O	Ascending and descending PEEP (20 min of each PEEP 0, 5, 10cmH2O or alternate).	1	0, 5, 10	8	N	Isoflurane		VCV
Leong et al, 2007[44]	No PEEP	PEEP 5, 8, 10 cmH_2O	1	0, 5, 8, 10	7-9	N	Isoflurane		PCV

(Continued)

THOR

TABLE E1. Continued

Article	Control intervention	Experimental intervention	FiO_2	PEEP cmH_2O	TV, mL/kg	Recruitment maneuver	Anesthetic	Thoracic epidural	Ventilator mode
Senturk et al, 2005[48]	No PEEP	PEEP 4 cmH_2O	1	0, 4	719 ± 121 mL	N	Propofol TIVA	Thoracic epidural (placed, not used)	PCV
Spadaro et al, 2018[35]	No PEEP	PEEP 5, 10 cmH_2O		0, 5, 10	5	N	Propofol TIVA + remifentanil	Thoracic epidural	VCV
Tusman et al, 2004[51]	No recruitment	PIP and PEEP were sequentially increased from 30/10 cmH_2O to 35/15 cmH_2O in steps of 5 breaths. The recruitment pressure of 40/20 cmH_2O was applied for 10 breaths.	1	8	6	Y	Isoflurane	Thoracic Epidural	VCV
Valenza et al, 2004[45]	No PEEP	PEEP 10 cmH_2O	0.6	0, 10	10	N	Isoflurane		VCV
Mascotto et al, 2003[46]	No PEEP	PEEP 4.3 ± 2 cmH_2O	0.5	0, 4	9	N	Isoflurane	Thoracic epidural	
Tusman et al, 2002[39]	No recruitment	PIP and PEEP were increased stepwise from 30/10 to 35/15 in steps of 12 breaths, and finally 40/20 cm H_2O at an I:E of 1:1.	1	5	6	Y	Isoflurane	Thoracic epidural	VCV
Abe et al, 1998[47]	No PEEP	PEEP 4, 8 cmH_2O treated with either sevoflurane or isoflurane	1	0, 4, 8	10	N	Isoflurane or sevoflurane	Thoracic epidural (placed, not used)	VCV

Senturk and colleagues[48] (2005) employ a ventilation protocol with variable TV and report TV as an outcome in each group. TVs were similar in control and experimental groups and correspond approximately to 10 mL/kg if 70k g is estimated. *FiO_2*, Fraction of inspired oxygen during OLV; *PEEP*, positive end-expiratory pressure; *TV*, tidal volume; *OLV*, one-lung ventilation; *Y*, yes, recruitment maneuver performed; *VCV*, volume control ventilation; *TIVA*, total intravenous anesthetic; *PIP*, peak inspiratory pressure; *PCV*, pressure control ventilation; *N*, no recruitment maneuver performed; *TLV*, Two-lung ventilation.

TABLE E2. Risk of bias assessment

Study	Study design	Total no. participants	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Selection	Comparability	Outcome	N-O total score
Recruitment maneuvers												
Choi et al, 2015[36]	RCT	99	L	L	H	H	L	L				
Unzueta et al, 2012[38]	RCT	40	L	H	H	H	L	L				
Park et al, 2011[37]	RCT	42	L	L	H	H	L	L				
Tusman et al, 2004[51]	Crossover trial	12							3	0	3	6
Tusman et al, 2002[39]	Crossover trial	10							1	1	3	7
PEEP												
Park et al, 2019[41]	RCT	292	L	L	L	L	L	L				
Rauseo et al, 2018[49]	Case series	13							3	0	3	6
Choi et al, 2015[36]	RCT	99	L	L	H	H	L	L				
Ferrando et al, 2014[42]	RCT	33	U	H	H	H	L	L				
Hoftman et al, 2011[50]	Crossover trial	41							4	0	3	7
Ren et al, 2008[43]	RCT	30	U	H	H	H	L	L				
Leong et al, 2007[44]	RCT	42	L	L	H	H	L	L				
Senturk et al, 2005[48]	Crossover trial	25							3	1	3	8
Spadaro et al, 2018[35]	Crossover trial	41							3	1	3	
Valenza et al, 2004[45]	RCT	46	U	L	H	H	L	L				
Mascotto et al, 2003[46]	RCT	50	L	H	H	L	L	L				
Abe et al, 1998[47]	RCT	20	L	H	H	H	L	U				

The Cochrane Risk of Bias tool assigns a score of high risk, uncertain risk, or low risk to each of 6 categories (random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting). The modified N-O assigns up to 10 stars for criteria in 3 domains (patient selection, comparability between groups, methods of outcome assessment). *N-O*, Newcastle-Ottawa Score; *RCT*, randomized controlled trial; *L*, low risk of bias; *H*, high risk of bias; *PEEP*, positive end-expiratory pressure; *U*, uncertain risk of bias.