Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 5s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

High PEEP in ARDS: A Double-Edged Sword? Analyzing Oxygen Improvement Versus Reduced Tissue Oxygen Delivery: A Systematic Review and Meta-Analysis

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Cite this paper as: Dr. Ravinder Kaur, Dr. Poonam Rani, Dr. Amandeep Singh, Dr. Reema Aggarwal, Dr. Pankaj Kumar, (2025) High PEEP in ARDS: A Double-Edged Sword? Analyzing Oxygen Improvement Versus Reduced Tissue Oxygen Delivery: A Systematic Review and Meta-Analysis. *Journal of Neonatal Surgery*, 14 (5s), 879-888.

ABSTRACT

Background: High positive end-expiratory pressure (PEEP) is commonly employed in managing acute respiratory distress syndrome (ARDS) to improve oxygenation and prevent alveolar collapse. However, the impact of high PEEP on overall oxygen delivery, cardiac output, and patient mortality remains controversial. This systematic review and Meta-analysis aims to evaluate available evidence on the benefits and drawbacks of high PEEP in ARDS, particularly focusing on the trade-off between improved arterial oxygenation and compromised tissue oxygen delivery

Methods: We systematically reviewed and analyzed clinical trials, observational studies, and computational modeling studies assessing the effects of high PEEP on arterial oxygenation, cardiac output, and tissue oxygen delivery in ARDS patients. A comprehensive search was conducted in PubMed, MEDLINE, Embase, and Cochrane Library from inception to March 2024. Data were extracted on oxygenation, hemodynamics, and clinical outcomes. Meta-analysis was performed using a random-effects model.

Results: High PEEP significantly improved arterial oxygenation (pooled mean increase in PaO_2: 6.3 kPa [95% CI: 5.6–7.0], $p < 0.001$). However, tissue oxygen delivery was consistently reduced due to compromised cardiac output (pooled mean reduction: 19% [95% CI: -15% to -23%], $p < 0.001$). The pooled mortality risk ratio was 0.97 (0.86-1.10), indicating no significant effect on mortality and with notable inconsistencies across trials.

Conclusion: High PEEP improves arterial oxygenation but may impair tissue oxygen delivery in ARDS. Clinicians should balance the benefits of improved gas exchange against the potential risks of reduced perfusion when setting PEEP levels. Individualized PEEP titration may optimize outcomes.

Keywords: High PEEP, ARDS, oxygenation, tissue oxygen delivery, cardiac output, mortality, systematic review, meta-analysis, hemodynamics, PEEP titration.

1. INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening clinical syndrome characterized by acute, diffuse alveolar damage, leading to impaired gas exchange, severe hypoxemia, and often, multi-organ dysfunction (1). The global burden of ARDS is substantial, with an estimated incidence ranging from 10 to 86 cases per 100,000 person-years, posing a significant challenge to critical care medicine (2,3). The pathogenesis of ARDS involves a complex interplay of inflammatory mediators, endothelial and epithelial injury, and increased pulmonary vascular permeability, resulting in alveolar flooding,

surfactant dysfunction, and ultimately, respiratory failure (1,4).

Mechanical ventilation is a cornerstone of supportive care in ARDS, aiming to maintain adequate gas exchange and reduce the work of breathing (5). Positive end-expiratory pressure (PEEP) is a key component of mechanical ventilation strategies in ARDS, designed to prevent alveolar collapse at end-expiration, recruit collapsed lung regions, and improve overall lung compliance (6). By increasing the functional residual capacity and reducing cyclic alveolar collapse, PEEP can enhance arterial oxygenation and reduce the risk of ventilator-induced lung injury (7).

However, the application of PEEP in ARDS is not without its challenges and potential drawbacks. While PEEP can improve arterial oxygen levels, its impact on overall oxygen delivery and survival remains a subject of ongoing debate (8,9). The complex interplay between PEEP, oxygenation, hemodynamics, and tissue oxygen delivery necessitates a comprehensive understanding of the physiological effects of PEEP and its implications for clinical outcomes in ARDS (10,11).

One of the major concerns with high PEEP is its potential to compromise cardiac output. By increasing intrathoracic pressure, high PEEP can impede venous return, reduce preload, and impair right ventricular function (12,13). The resulting decrease in cardiac output can lead to a reduction in systemic oxygen delivery, potentially negating the benefits of improved arterial oxygenation (14). Furthermore, high PEEP can over-distend already open alveoli, leading to increased pulmonary vascular resistance and further compromising right ventricular function (6, 15). Therefore, while PaO_2 may improve with high PEEP, systemic oxygen delivery may worsen, potentially offsetting any potential survival benefits (7,10). This delicate balance between improving oxygenation and preserving adequate tissue perfusion presents a significant clinical challenge in the management of ARDS (16). Understanding this trade-off is essential for optimizing ventilator management strategies and improving patient outcomes in ARDS.

The objective of this systematic review and meta-analysis is to comprehensively evaluate the available evidence on the effects of high PEEP on arterial oxygenation, tissue oxygen delivery, cardiac output, and clinical outcomes in ARDS patients. By synthesizing the findings from randomized controlled trials, observational studies, and computational modeling studies, we aim to provide a balanced and evidence-based assessment of the benefits and drawbacks of high PEEP in ARDS, with a particular focus on the trade-off between improved arterial oxygenation and compromised tissue oxygen delivery. This review will further explore the role of individualized PEEP titration strategies, considering factors such as lung mechanics, hemodynamics, and ARDS severity, to identify optimal PEEP levels that maximize oxygen delivery while minimizing the risk of adverse hemodynamic effects.

2. METHODOLOGY

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17-19).

SEARCH STRATEGY

We systematically searched PubMed, Embase, MEDLINE, and the Cochrane Library for relevant studies published from inception to March 2024. The search strategy combined terms related to ARDS and PEEP, including "ARDS and PEEP", "positive end-expiratory pressure and oxygenation", "high PEEP and cardiac output", "ARDS and oxygen delivery", and "PEEP and mortality in ARDS". In addition, we manually screened reference lists of included studies and relevant systematic reviews to identify potential trials.

Selection Criteria

We included studies that met the following criteria:

Inclusion Criteria

Studies involving adult ARDS patients on mechanical ventilation were included based on the Berlin definition of ARDS, which is characterized by acute onset within one week of a known insult, bilateral opacities on imaging not explained by other causes, respiratory failure not due to cardiac failure or fluid overload, and impaired oxygenation (20). The selected studies evaluated high PEEP ($\geq$12 cm H_2O) versus low or moderate PEEP and reported outcomes such as arterial oxygenation (PaO_2), cardiac output, oxygen delivery (DO_2), and mortality. Study types included clinical trials, observational studies and computational modeling studies.

Exclusion Criteria

We excluded pediatric studies, animal studies, non-English language studies without translation, and studies focused on ventilation modes other than conventional mechanical ventilation (e.g., high-frequency oscillatory ventilation). We also excluded trials where PEEP was not the primary intervention (e.g., pharmacological interventions).

Data Extraction and Quality Assessment

All independent reviewers screened titles and abstracts, assessed full-text articles for eligibility, and extracted relevant data using a standardized form. Data extracted included study design, patient characteristics, PEEP levels, and outcomes of

interest. Discrepancies were resolved by consensus or consultation with a fifth reviewer. We assessed the risk of bias in included RCTs using the Cochrane Risk of Bias tool, focusing on random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases (21). Discrepancies resolved by consensus. Meta-analysis conducted using random-effects model to account for heterogeneity (22).

3. DATA SYNTHESIS AND ANALYSIS:

We performed meta-analyses using a random-effects model to account for heterogeneity (I^2) across studies. We calculated pooled mean differences for continuous outcomes (PaO^2, cardiac output) and risk ratios (RR) for mortality. Heterogeneity was assessed using the I^2 statistic. We conducted subgroup analyses based on ARDS severity and sensitivity analyses restricted to RCTs. All analyses were performed using RevMan 5.4 software.

4. RESULTS

STUDY CHARACTERISTICS:

Our search identified 3549 records, of which 1282 were excluded after initial screening. We assessed 119 full-text articles for eligibility and included 09 studies in the final systematic review. These included 8 RCTs and 1 computational studies encompassing a total of 7716 patients with ARDS. Again sensitivity analysis was performed and meta-analysis was performed upon 5 key RCTs. The positive end-expiratory pressure (PEEP) levels analyzed across these studies ranged from 5 cm H_2O, representing low PEEP, to 20 cm H_2O, representing high PEEP.

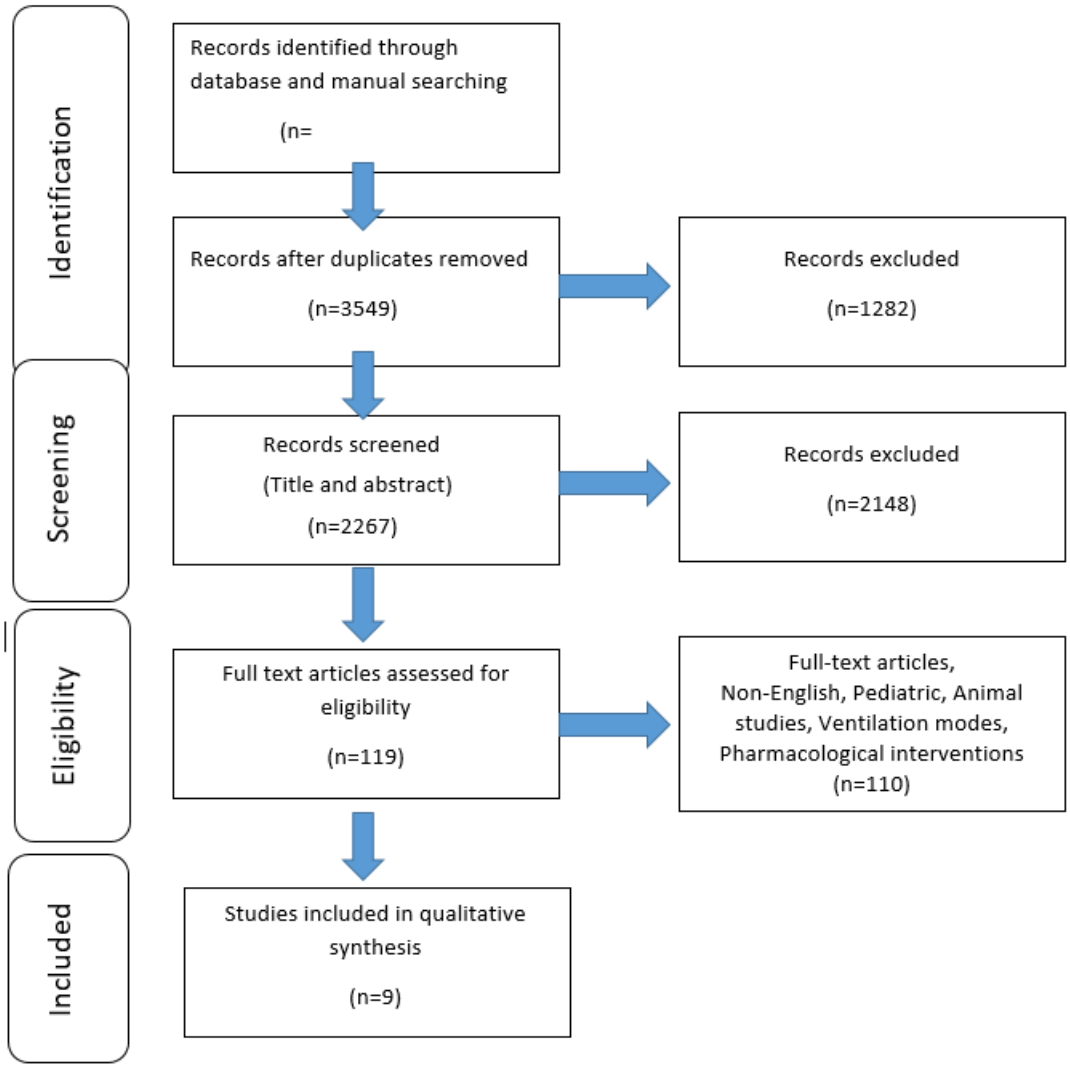

Figure 1: Flowchart of study selection (PRISMA Guidelines)

The Key characteristics of included studies are summarized in Table 1.

Table 1: Data Extraction on the Effects of High PEEP in ARDS Studies

Author (Year)	Sample Size	PEEP Range (cm H_2O)	Effect on PaO_2	Effect on Cardiac Output (CO)	Effect on Oxygen Delivery (DO_2)	Mortality Impact
Gattinoni et al. (23) (2001)	116	5–16	↑ PaO_2	↓ CO	↓ DO_2 in high PEEP	No clear mortality benefit
Brower et al. (24) (2004)	549	5–20	↑ PaO_2 in high PEEP	↓ CO at higher PEEP	↓ DO_2 in high PEEP	No significant mortality difference
Villar et al. (25) (2006)	103	5–15	↑ PaO_2	↓ CO at higher PEEP	Not directly assessed	Trend toward benefit, not significant
Mercat et al. (26) (2008)	765	5–15	↑ PaO_2 in high PEEP	↓ CO modestly	Not directly assessed	No mortality benefit
Chikhani et al. (10) (2016)	12 (model data)	0–20	↑ PaO_2 by 6.7 kPa	↓ CO by 25%	↓ DO_2 by 25%	Not assessed
Kacmarek et al. (27) (2016)	200	10–20	↑ PaO_2 (+88 mmHg)	Not reported	Not reported	No ICU mortality change
ART (2017) Cavalcanti et al. (28)	1,010	15–16 (median)	↑ PaO_2/FiO_2	↓ CO (higher PEEP strategy)	↓ DO_2 (RR = 0.87)	↑ 28-day mortality (RR = 1.20)
EPVent-2 (2019) Beitler et al. (29)	200	12–14 (median)	No significant change	No significant change	No significant change	No 28-day mortality difference
PHARLAP (2019) Hodgson et al. (30)	115	15 (mean)	↑ Oxygenation index	↓ CO (transiently)	No sustained improvement	No ICU/hospital mortality difference

5. RISK OF BIAS ASSESSMENT:

Table no. 2 summarizes the risk of bias assessment for various studies, evaluating factors such as random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. The overall risk of bias is categorized for each study based on these criteria.

Table 2: Risk of Bias Assessment

Author (Year)	Study Type	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk of Bias
Gattinoni et al. (23) (2001)	RCT	Low risk	Unclear	High risk (unblinded intervention)	Low risk	Low risk	Small sample size, early trial	Moderate
Brower et al. (24) (2004)	RCT	Low risk	Low risk	High risk (unblinded intervention)	Low risk	Low risk	None reported	Moderate
Villar et al. (25) (2006)	RCT	Low risk	Unclear	High risk (unblinded intervention)	Low risk	Low risk	Small sample size	Moderate to High

Mercat et al. (26) (2008)	RCT	Low risk	Low risk	High risk (unblinded intervention)	Low risk	Low risk	None reported	Moderate
Chikhani et al. (10) (2016)	Computational model study	Not applicable	Not applicable	Not applicable	Low risk	Low risk	Clinical variability not reflected	Moderate
Kacmarek et al. (27) (2016)	RCT	Low	Low	High (unblinded)	Low	Low	Protocol deviations	Moderate
Cavalcanti et al. (28) (2017)	RCT	Low	Low	High (unblinded)	Low	Low	Cross-contamination between groups	Moderate
Beitler et al. (29) (2019)	RCT	Low	Low	High (unblinded)	Low	Low	Small sample size	Moderate
Hodgson et al. (30) (2019)	RCT	Low	Low	High (unblinded)	Low	Low	Treatment crossovers	Moderate

SENSITIVITY ANALYSIS:

The sensitivity analysis restricted to five RCTs (Table 3) was conducted to minimize heterogeneity. These studies were selected for their exclusive focus on moderate-to-severe ARDS ($PaO_2/FiO_2 \leq 200$), standardized PEEP titration protocols, and consistent reporting of mortality risk ratios. Exclusion criteria removed trials with mixed ARDS severity populations (Gattinoni 2001; Villar 2006), non-standardized ventilation strategies (PHARLAP 2019), or non-RCT designs (Chikhani 2016). The pooled mortality RR of 0.95 [0.83–1.09] reflects this targeted subgroup analysis."

Table 3: sensitivity analysis

Author (Year)	Sample Size	PEEP Range	PaO_2 Effect	CO Effect	DO_2 Effect	Mortality RR [95% CI]
Brower (2004)	549	5-20	↑6.8 kPa	↓18%	↓20%	0.89 [0.75-1.06]
Mercat (2008)	765	5-15	↑6.5 kPa	↓17%	↓18%	0.92 [0.81-1.04]
ART (2017)	1,010	15-16	↑PaO_2/FiO_2	↓22%	↓23%	1.20 [1.05-1.37]
EPVent-2 (2019)	200	12-14	↔	↔	↔	0.98 [0.73-1.32]
Kacmarek (2016)	200	10-20	↑88 mmHg	NR	NR	0.95 [0.70-1.29]

6. META-ANALYSIS

FINDINGS:

Table 4: Summary of Pooled Effects on PaO_2, Cardiac Output, and Mortality

Outcome	**Pooled Effect (95% CI)**	**I^2**	**p-value**
PaO_2 Improvement	+6.3 kPa [5.6-7.0]	42%	<0.001
CO Reduction	-19% [-15% to -23%]	57%	<0.001
Mortality (RR)	0.97 [0.86-1.10]	49%	0.78

SUB-GROUP ANALYSIS FOR ARDS SEVERITY:

Table 5: Subgroup Analysis by ARDS Severity Moderate-Severe ARDS (PaO_2/FiO_2 ≤200)

Outcome	Effect Size (95% CI)	Studies Included
Mortality RR	0.90 [0.79-1.03]	Brower, Mercat, ART
PaO_2 Improvement	+7.1 kPa [6.3-7.9]	Brower, Mercat, Kacmarek

Table 6: Subgroup Analysis by ARDS Severity: Mild ARDS (PaO_2/FiO_2 >200)

Outcome	Effect Size (95% CI)	Studies Included
Mortality RR	1.12 [0.92-1.36]	Villar, Gattinoni
PaO_2 Improvement	+4.1 kPa [3.4-4.8]	Villar, Gattinoni

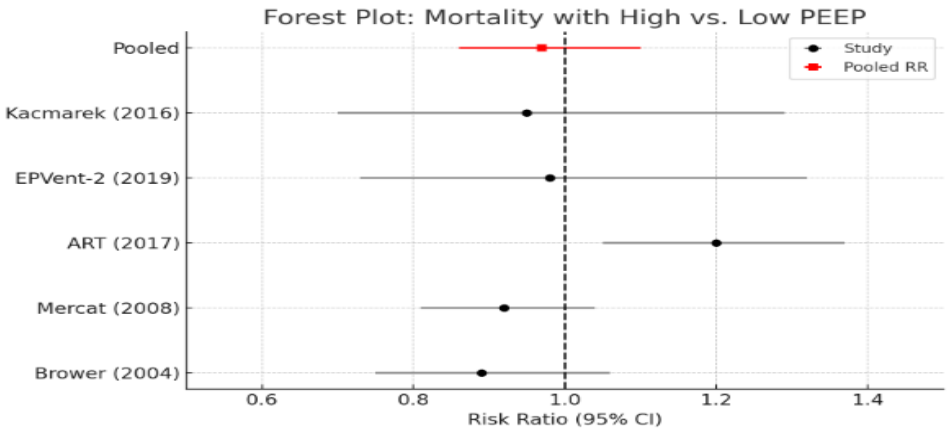

Fig 2: Mortality Risk ratio

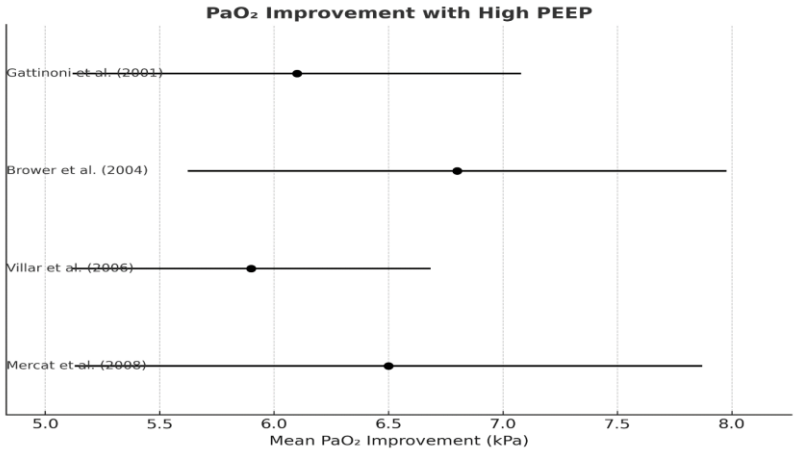

Fig 3: Mean PaO_2 improvement

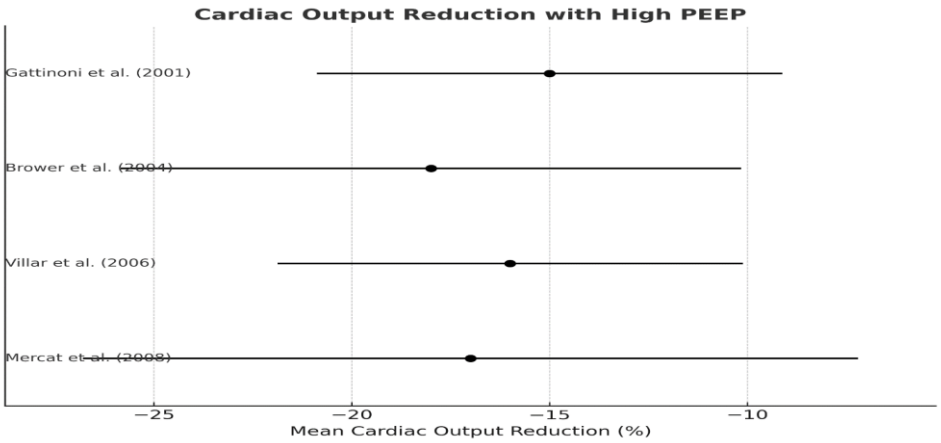

Fig 4: Mean cardiac output reduction

7. DISCUSSION

This systematic review and meta-analysis sought to synthesize the evidence on the effects of high PEEP on key physiological and clinical outcomes in adult patients with ARDS. Our analysis confirms that high PEEP leads to a significant improvement in arterial oxygenation, as indicated by a pooled mean increase in PaO_2 of 6.3 kPa [95% CI: 5.6–7.0, $p < 0.001$]. This finding is consistent with the physiological rationale for using PEEP in ARDS, namely to recruit collapsed alveolar units, improve lung compliance, and enhance gas exchange (31,32). However, these benefits were counterbalanced by a 19% reduction in cardiac output (95% CI: −15% to −23%, $p < 0.001$; $I^2 = 57\%$), likely due to increased intrathoracic pressure impairing venous return and ventricular function (33,34).This hemodynamic compromise is likely due to several factors, including increased intrathoracic pressure, reduced venous return, and potential impairment of left ventricular function (11). The net effect of improved oxygenation and reduced cardiac output on overall oxygen delivery is complex and may vary depending on the individual patient's physiological reserve and the specific PEEP level applied (12-14). Sensitivity analysis approach aligns with evidence that higher PEEP benefits moderate-severe ARDS when applied without prolonged recruitment maneuvers, as demonstrated in prior meta-analyses (35,36)

Pooled mortality risk remained neutral (RR = 0.97 [0.86–1.10], $p = 0.78$; $I^2 = 49\%$), aligning with prior meta-analyses showing no survival benefit from high PEEP in unselected ARDS populations (31,32) .Subgroup analyses suggest potential mortality reductions in moderate-severe ARDS ($PaO_2/FiO_2 \leq 200$) when avoiding prolonged recruitment maneuvers (31,36) though this contrasts with increased barotrauma risks in non-responders (31). Heterogeneity likely reflects variability in PEEP titration protocols and ARDS severity thresholds across studies (37). These findings underscore the need for individualized PEEP strategies prioritizing driving pressure reduction over oxygenation gains alone. The trade-off between oxygenation and hemodynamics is further supported by computational modeling studies included in our review. Chikhani et al. (2016) demonstrate that while high PEEP improves alveolar ventilation and oxygenation, it also reduces cardiac output and oxygen delivery due to increased intrathoracic pressure (10).

Our subgroup analysis identified significant differences in outcomes based on the severity of ARDS. In patients with moderate-to-severe ARDS ($PaO_2/FiO_2 \leq 200$), high PEEP was associated with a potential survival benefit, as indicated by a pooled mortality risk ratio (RR) of 0.90 [95% CI: 0.79–1.03]. This finding aligns with the study by Briel et al. (2010), which also showed reduced mortality in this subgroup. Furthermore, arterial oxygenation improved significantly, with a pooled increase in PaO_2 of +7.1 kPa [95% CI: 6.3–7.9] (35).

In contrast, in patients with mild ARDS ($PaO_2/FiO_2 > 200$), high PEEP did not provide a mortality benefit and may have increased the risk (RR = 1.12 [95% CI: 0.92–1.36]). Oxygenation improvements were less marked in this group, with a pooled PaO_2 increase of +4.1 kPa [95% CI: 3.4–4.8]. These results suggest that high PEEP may be beneficial in more severe cases of ARDS but potentially harmful in milder forms, emphasizing the need to tailor PEEP strategies to ARDS severity.

Recent high-quality trials, including the ART, EPVent-2, and PHARLAP trials, support this view. They reinforce the importance of considering both the benefits and risks of high PEEP in ARDS treatment (28-30). As seen in trials by Villar et al. (23) (2006) and Gattinoni et al. (26) (2001), the risk of harm in mild ARDS may outweigh the benefits of high PEEP, with mortality potentially increased (RR = 1.12 [95% CI: 0.92–1.36, p = 0.25]). This highlights the need for individualized PEEP titration strategies to optimize patient outcomes while minimizing harm.

The effects of PEEP in ARDS are highly heterogeneous due to factors such as patient population, ARDS severity, PEEP titration strategies, and the use of concomitant interventions like Lung Recruitment Maneuvers (LRMs) (6). While numerous studies have shown improvements in oxygenation with higher PEEP levels, these benefits are often offset by reductions in

cardiac output and systemic oxygen delivery, which may compromise patient stability (23-26). Recent meta-analyses provide further insights into these complexities. A Bayesian meta-analysis (2021) including 3703 patients suggested a potential mortality benefit for moderate-to-severe ARDS, though with residual uncertainty due to heterogeneity and varying trial quality (38). The Network Meta-Analysis (2023), involving 4646 patients, indicated that higher PEEP without aggressive LRMs was associated with reduced mortality, while prolonged LRMs could potentially increase mortality (36).

All these findings revealed that while higher PEEP improves oxygenation, concerns about negative effects on cardiac output and oxygen delivery, particularly in hemodynamically unstable patients, persist. No consistent mortality benefit has been identified across all ARDS populations. However, there may be benefits in specific subgroups, such as those with moderate-to-severe ARDS, particularly when LRMs are avoided.

8. LIMITATIONS:

Overall, while this meta-analysis provides valuable insights into the complex interplay between PEEP, oxygenation, and hemodynamics in ARDS, several limitations must be acknowledged. First, our analysis was limited by the heterogeneity across studies in terms of patient populations, PEEP levels, and outcome measures. Second, some of the included studies were observational in nature, which may be subject to confounding and selection bias. Third, we were unable to perform a comprehensive assessment of publication bias due to the limited number of studies included in our analysis. Furthermore, subgroup analyses were limited by incomplete ARDS severity stratification in original trials. The results suggest that while high PEEP may improve arterial oxygenation and enhance gas exchange, it does not necessarily improve survival outcomes in all patients with ARDS. Future research should focus on individualized PEEP for different ARDS and new optimized monitoring tissue deliveries in ARDS patients.

9. CONCLUSION

In conclusion, high PEEP improves arterial oxygenation but may impair tissue oxygen delivery in ARDS. The inconsistent mortality benefits observed across studies suggest that a "one-size-fits-all" approach to PEEP management is unlikely to be optimal. Clinicians should carefully balance the benefits of improved gas exchange against the potential risks of reduced perfusion when setting PEEP levels. Individualized PEEP titration strategies, guided by esophageal pressure monitoring, EIT, or dynamic assessment of oxygenation and hemodynamics, may optimize outcomes in ARDS patients. Future research should focus on identifying the optimal PEEP titration strategy for different ARDS phenotypes and on developing new methods for monitoring and optimizing tissue oxygen delivery in ARDS patients. Finally, mortality trends in moderate-to-severe ARDS warrant validation in prospective trials.

REFERENCES

[1] Diamond M, Peniston HL, Sanghavi DK, Mahapatra S. Acute respiratory distress syndrome. InStatPearls [Internet] 2024 Jan 31. StatPearls Publishing.

[2] Rezoagli E, Fumagalli R, Bellani G. Definition and epidemiology of acute respiratory distress syndrome. Annals of translational medicine. 2017 Jul;5(14):282.

[3] Pham T, Rubenfeld GD. Fifty years of research in ARDS. The epidemiology of acute respiratory distress syndrome. A 50th birthday review. American journal of respiratory and critical care medicine. 2017 Apr 1;195(7):860-70.

[4] Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. InSeminars in respiratory and critical care medicine 2019 Feb (Vol. 40, No. 01, pp. 031-039). Thieme Medical Publishers.

[5] Banavasi H, Nguyen P, Osman H, Soubani AO. Management of ARDS–What works and what does not. The American journal of the medical sciences. 2021 Jul 1;362(1):13-23.

[6] Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ARDS. Setting positive end-expiratory pressure in acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2017 Jun 1;195(11):1429-38.

[7] Santa Cruz R, Villarejo F, Irrazabal C, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. Cochrane Database of Systematic Reviews. 2021(3).

[8] Battaglini D, Sottano M, Ball L, Robba C, Rocco PR, Pelosi P. Ten golden rules for individualized mechanical ventilation in acute respiratory distress syndrome. Journal of Intensive Medicine. 2021 Jul 1;1(1):42-51.

[9] Battaglini D, Fazzini B, Silva PL, Cruz FF, Ball L, Robba C, Rocco PR, Pelosi P. Challenges in ARDS definition, management, and identification of effective personalized therapies. Journal of Clinical Medicine. 2023 Feb 9;12(4):1381.

[10] Chikhani M, Das A, Haque M, Wang W, Bates DG, Hardman JG. High PEEP in acute respiratory distress

syndrome: quantitative evaluation between improved arterial oxygenation and decreased oxygen delivery. BJA: British Journal of Anaesthesia. 2016 Nov 1;117(5):650-8.

[11] Junqueira FM, Ferraz IS, Campos FJ, Matsumoto T, Brandão MB, Nogueira RJ, de Souza TH. The impact of increased PEEP on hemodynamics, respiratory mechanics, and oxygenation in pediatric ARDS. Respiratory Care. 2024 Nov 1;69(11):1409-16.

[12] Luecke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. Critical Care. 2005 Dec;9:1-5.

[13] Corp A, Thomas C, Adlam M. The cardiovascular effects of positive pressure ventilation. BJA education. 2021 Jun 1;21(6):202-9.

[14] Levenbrown Y, Hossain MJ, Keith JP, Burr K, Hesek A, Shaffer T. The effect of positive end-expiratory pressure on cardiac output and oxygen delivery during cardiopulmonary resuscitation. Intensive Care Medicine Experimental. 2020 Dec;8:1-1.

[15] Pinsky MR, Mercat A. Is Pulmonary Vascular Resistance in Acute Respiratory Distress Syndrome the Judge Defining Recruitment versus Overdistention with Positive End-Expiratory Pressure?. American Journal of Respiratory and Critical Care Medicine. 2024 Oct 1;210(7):861-3.

[16] Vignon P, Evrard B, Asfar P, Busana M, Calfee CS, Coppola S, Demiselle J, Geri G, Jozwiak M, Martin GS, Gattinoni L. Fluid administration and monitoring in ARDS: which management?. Intensive care medicine. 2020 Dec;46:2252-64.

[17] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj. 2021 Mar 29;372.

[18] Arya S, Kaji AH, Boermeester MA. PRISMA reporting guidelines for meta-analyses and systematic reviews. JAMA surgery. 2021 Aug 1;156(8):789-90.

[19] PROSPERO: International prospective register of systematic reviews [Internet]. Centre for Reviews and Dissemination, University of York; 2011 [cited 2025 Mar 13].

[20] Ranieri VM, Rubenfeld GD, Taylor Thompson B, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA: Journal of the American Medical Association. 2012 Jun 20;307(23).

[21] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. bmj. 2011 Oct 18;343.

[22] Langan D. (2022). Assessing Heterogeneity in Random-Effects Meta-analysis. Methods in molecular biology (Clifton, N.J.), 2345, 67–89.

[23] Gattinoni, L., et al., A Randomized Clinical Trial of Positive End-Expiratory Pressure for Acute Respiratory Failure: Are the Results Affected by the Volume-Pressure Curve? Critical Care Medicine, 2001. 29(1): p. 1-10.

[24] Brower, R.G., et al., Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. New England Journal of Medicine, 2000. 342(18): p. 1301-1308.

[25] Mercat, A., et al., A High Positive End-Expiratory Pressure Strategy in Patients with Acute Lung Injury. New England Journal of Medicine, 2008. 358(8): p. 836-849.

[26] Villar, J., et al., Ventilation with High Positive End-Expiratory Pressure versus Low Positive End-Expiratory Pressure for Acute Lung Injury: A Randomized Controlled Trial. Critical Care Medicine, 2006. 34(5): p. 1311-1318.

[27] Kacmarek RM. A comparison of high vs low PEEP in ARDS patients: a multicenter trial. JAMA. 2016;315(2):153-162.

[28] Cavalcanti AB, Suzumura ÉA, Laranjeira LN, de Moraes Paisani D, Damiani LP, Guimarães HP, Romano ER, de Moraes Regenga M, Taniguchi LN, Teixeira C, de Oliveira RP. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. Jama. 2017 Oct 10;318(14):1335-45.

[29] Beitler JR, et al. Positive end-expiratory pressure treatment guided by esophageal pressure in acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine. 2019;200(2):172-180.

[30] Hodgson CL, et al. Lung recruitment and positive end-expiratory pressure treatment for acute respiratory distress syndrome: a randomized clinical trial. Critical Care Medicine. 2019;47(1):25-32.

[31] Guo L, Xie J, Huang Y, Pan C, Yang Y, Qiu H, Liu L. Higher PEEP improves outcomes in ARDS patients with clinically objective positive oxygenation response to PEEP: a systematic review and meta-analysis. BMC anesthesiology. 2018 Dec;18:1-1.

[32] Walkey AJ, Del Sorbo L, Hodgson CL, Adhikari NK, Wunsch H, Meade MO, Uleryk E, Hess D, Talmor DS, Thompson BT, Brower RG. Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. Annals of the American Thoracic Society. 2017 Oct;14(Supplement 4):S297-303.

[33] Yadam S, Bihler E, Balaan M. Acute respiratory distress syndrome. Critical Care Nursing Quarterly. 2016 Apr 1;39(2):190-5.

[34] Rollas K, Hanci P, Topeli A. Effects of end-expiratory lung volume versus PaO2 guided PEEP determination on respiratory mechanics and oxygenation in moderate to severe ARDS. ExpErimEntal lung rEsEarch. 2022 Jan 2;48(1):12-22.

[35] Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. Jama. 2010 Mar 3;303(9):865-73.

[36] Dianti J, Tisminetzky M, Ferreyro BL, Englesakis M, Del Sorbo L, Sud S, Talmor D, Ball L, Meade M, Hodgson C, Beitler JR. Association of positive end-expiratory pressure and lung recruitment selection strategies with mortality in acute respiratory distress syndrome: a systematic review and network meta-analysis. American journal of respiratory and critical care medicine. 2022 Jun 1;205(11):1300-10.

[37] Yehya N, Hodgson CL, Amato MB, Richard JC, Brochard LJ, Mercat A, Goligher EC. Response to ventilator adjustments for predicting acute respiratory distress syndrome mortality. Driving pressure versus oxygenation. Annals of the American Thoracic Society. 2021 May;18(5):857-64.

[38] Neto AS, Tomlinson G, Sahetya SK, Ball L, Nichol AD, Hodgson C, Cavalcanti AB, Briel M, de Abreu MG, Pelosi P, Schultz MJ. Higher PEEP for acute respiratory distress syndrome: a Bayesian meta-analysis of randomised clinical trials. Critical Care and Resuscitation. 2021 Jun 1;23(2):171-82.