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INFOGRAPHIC

ORIGINAL ARTICLE

Determination of positive end-expiratory pressure in COVID-19-related acute respiratory distress syndrome

A systematic review

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BACKGROUND The impact of high positive end-expiratory pressure (PEEP) ventilation and the optimization of PEEP titration in COVID-19-induced acute respiratory distress syndrome (ARDS) continues to be a subject of debate. In this systematic review, we investigated the effects of varying PEEP settings on patients with severe ARDS primarily resulting from COVID-19 (C-ARDS).

OBJECTIVES Does higher or lower PEEP improve the outcomes in COVID-19 ARDS? Does individually titrated PEEP lead to better outcomes compared with PEEP set by standardised (low and high ARDS network PEEP tables) approaches? Does the individually set PEEP (best PEEP) differ from PEEP set according to the standardised approaches (low and high ARDS network PEEP tables)?

DESIGN Systematic review of observational studies without metaanalysis.

DATA SOURCES We performed an extensive systematic literature search in Cochrane COVID-19 Study Register (CCSR), PubMed, Embase.com, Web of Science Core Collection, World Health Organization COVID-19 Global literature on coronavirus disease, World Health Organization International Clinical Trials Registry Platform (ICTRP), medRxiv, Cochrane Central Register of Controlled Trials until 24/01/2024.

ELIGIBILITY CRITERIA Ventilated adult patients (≧18 years) with C-ARDS.

RESULTS We screened 16 026 records, evaluated 119 full texts, and included 12 studies ($n = 1431$ patients) in our final data synthesis, none of them being a randomised controlled trial. The heterogeneity of study procedures and populations did not allow conduction of a meta-analysis. The results of those studies that compared lower and higher PEEP strategies in C-ARDS were ambiguous pointing out either positive effects on oxygenation with high levels of PEEP, or negative changes in lung mechanics.

CONCLUSION The available evidence does not provide sufficient guidance for recommendations on optimal PEEP settings in C-ARDS. In general, well designed platform studies are needed to answer the questions raised in this review and, in particular, to investigate the use of individualised PEEP titration techniques and the inclusion of patients with different ARDS entities, severities and disease stages.

TITLE REGISTRATION Our systematic review protocol was registered with the international prospective register of systematic reviews (PROSPERO 2021: CRD42021260303).

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KEY POINTS

- There is no consensus on the methodological approach to PEEP titration and a lack of well designed prospective RCTs that provide the necessary evidence for the optimal PEEP strategy in C-ARDS patients.
- Low-quality evidence suggests that C-ARDS patients should not primarily be ventilated with a high PEEP as suggested by the ARDSnet high PEEP table.
- A promising alternative would be to better individualize PEEP settings in patients with ARDS, including those with C-ARDS. Although not fully confirmed by the reviewed studies, our personal opinion is that clinicians should consider individualised PEEP titration methods especially when standardised PEEP tables suggest higher PEEP settings?

Introduction

Rationale

In mechanically ventilated patients, positive end-expiratory pressure (PEEP) is applied to reopen unventilated alveoli (anatomical recruitment) and to prevent cyclic collapse, that is, repeated recruitment and de-recruitment of poorly or nonventilated lung areas during the ventilatory cycle. PEEP can promote lung recruitment, reduce mechanical stress, and consequently improve compliance, carbon dioxide excretion, and oxygenation. Moreover, the application of PEEP can provide functional recruitment by reducing ventilation/perfusion mismatch (functional shunt) and improve oxygenation.[1,2] On the other hand, ventilation with a high PEEP can contribute to ventilator-induced lung injury (VILI), by promoting hyperinflation.[3–8] Hence, establishing an optimal PEEP level is of paramount importance for ventilated patients.

Acute respiratory distress syndrome (ARDS) is a syndrome that affects heterogeneous disease patterns and populations with different levels of lung injury pathophysiology. Despite this fact, there are only generalised recommendations and these do not take into account the specificity of the population, the timing, or the severity of the disease. The most recent meta-analysis looking at PEEP in ARDS recommends ventilation with higher PEEP, but the results appear to be heterogeneous as the studies use different definitions of high and low PEEP and apply different methods of PEEP titration.[6,7,9] Recently published guidelines on ARDS leave the clinician with unanswered questions, as the evidence assessment on high or low PEEP concepts or an individualised approach remains confusing.[10] Recommendations for ventilating patients with severe COVID-19-associated acute respiratory distress syndrome (C-ARDS) have largely been based on evidence from non-COVID-19 ARDS,[11,12] and there is an ongoing debate if there are clinically relevant pathophysiological differences between C-ARDS and non-COVID-19 ARDS.[12–14]

Currently, it is unclear whether patients with C-ARDS in particular can benefit from a higher or a lower PEEP strategy and whether a standardised approach (ARDS network Tables[15]) is superior to individually determined settings based on respiratory mechanics (PEEP trials), regional lung ventilation determined by imaging [computed tomography of the chest (CT)], electrical impedance tomography (EIT) or other diagnostic tools.[16–18] The latest meta-analysis on PEEP in ARDS, which included 18 randomised controlled studies with 4646 participants, reported with a high level of evidence that lower PEEP strategy was associated with a higher median risk of mortality compared with a higher PEEP strategy.[6] However, this evidence is characterised by a high degree of clinical heterogeneity, and none of these studies considered COVID-19 ARDS a separate entity. A recent survey from Germany revealed significant heterogeneity in PEEP settings for C-ARDS.[8] Even current C-ARDS-related guidelines show substantial variation of PEEP recommendations.[19,20]

Objectives

We wished to identify, evaluate, and summarize the current evidence on PEEP settings in patients with C-ARDS, and to investigate this topic in a group of patients with a more homogeneous cause of ARDS. We also set out to specifically address the following objectives:

(1) Does higher or lower PEEP improve the outcomes in COVID-19 ARDS? (Short: higher vs. lower PEEP)
(2) Does individually titrated PEEP lead to better outcomes compared with PEEP set by standardised (low and high ARDS network PEEP tables) approaches? (Short: individualised PEEP vs. standardised PEEP)
(3) Does the individually set PEEP differ from PEEP set according to the standardised approaches (low and high ARDS network PEEP tables)? (Short: individualised PEEP determination)

Materials and methods

Eligibility criteria

The study protocol was registered with PROSPERO on 6/2021 (CRD42021260303); minor changes to the protocol were amended on August 2021. We searched various databases through 25 January 2024. Detailed information on the search strategy is provided in the electronic supplement (Appendix A, http://links.lww.com/EJAIC/A98).

We included the following study types

(1) randomised controlled trials (RCT)
(2) quasi-randomised controlled trials
(3) nonrandomised studies (controlled prospective studies, interrupted time series, cohort studies and case–control studies)
(4) commentaries, letters or editorials if they reported specific new data on PEEP-setting in COVID-19 patients.

Noninterventional studies and studies without clearly identified intervention or comparison of groups were excluded. Likewise, we did not include ongoing studies and preprints in our final analysis. However, for a list of registered ongoing studies, we have designed ESM Table 3. We only included articles in English and German.

We included studies investigating the following populations

(1) adult patients ($\geq$18 years) with C-ARDS requiring invasive mechanical ventilation.
(2) mixed ARDS populations (COVID-19 and non-COVID-19), if data on C-ARDS were presented independently and accessible for separate analysis (minimum sample size: $n=3$ participants for non-randomised studies).

We included studies with interventions of

(1) Low PEEP (intervention) vs. high PEEP (comparison) (objective 1)
(2) Individualised PEEP strategy (intervention) vs. standard approaches (comparison) (objectives 2 and 3)

'Low' and 'high' PEEP levels were defined as reported by their respective studies, we did not enforce a general definition for 'high' or 'low' PEEP because of the heterogeneity of study conditions.

Individualised PEEP strategies were defined as those that consider characteristics of gas exchange, respiratory mechanics (recruitment manoeuvres, PEEP titration, transpulmonary pressure monitoring and volumetric capnometry) or regional lung ventilation analysed by different imaging methods (CT, EIT and ultrasound) of the individual patient to determine the optimal PEEP level.

The low (Low-PEEP-Table) and high (High-PEEP-Table) ARDS-Network PEEP Tables[21] and strategies of fixed PEEP determination without consideration of individual patient characteristics, were regarded as standardised PEEP strategies.

Several studies performed a subgroup analysis according to the positive or negative effect of PEEP on gas exchange and respiratory mechanics. Patients who benefited from higher PEEP ventilation were defined as 'recruiters', and those with none or negative effects as 'nonrecruiters'. There was no general definition of lung recruitability used in all studies (Supplementary Table S3, http://links.lww.com/EJAIC/A101), which is why we refer to the definition of recruitability used by the authors.

Primary and secondary outcomes

We defined the following outcome parameters:

Primary outcomes

(1) All-cause mortality up to longest follow-up
(2) Clinical status up to longest follow-up
    (a) ICU and hospital discharge
    (b) Duration of mechanical ventilation
    (c) Need for prone positioning
    (d) Need for ECMO
(1) Treatment-specific serious adverse events (SAEs) (pneumothorax, acute organ dysfunction)

Secondary outcomes

(1) Gas exchange (P_aO_2, P_aCO_2, P_aO_2/FiO_2 ratio)
(2) Compliance
(3) Dead space ventilation
(4) Recruitability of lung parenchyma [different definitions possible: positive change in ventilation mechanics (increase in P_aO_2 und compliance and decrease in P_aCO_2), radiologic imaging (increase in aerated tissue under higher PEEP level), EIT (increase in aerated tissue under higher PEEP level)].

Selection process

We uploaded results of our literature search to Covidence,[22] an Internet-based program that facilitates study selection processes, mainly for systematic reviews. This included the following steps, which were independently performed by each of two authors (AS, DH): title/abstract screening, full-text screening and risk of bias assessment. The detailed procedure is fully described in Appendix A, http://links.lww.com/EJAIC/A98.

Risk-of-bias assessment

We included studies with representative and comparable intervention groups. Nonrandomised studies were included only if we had no major concerns about study participant selection and between-group confounding factors assessed as part of our risk of bias assessment. Controlled studies with a serious or critical risk of bias in the areas of participant selection and confounding and single-arm studies with a high risk of bias in each area were formally excluded (see Appendix A, http://links.lww.com/EJAIC/A98 for full risk of bias assessment). Methods that would be used if a meta-analysis would be possible are described in Appendix B, http://links.lww.com/EJAIC/A98.

Amendments to the review protocol

During the study selection process, we realised a lack of high-quality studies on the effect of PEEP on related outcome parameters. Therefore, we decided to add an overview of those studies of our full-text screening to the review, that primarily had been excluded because of high risk of bias, as the authors concluded that, as of now, some of the data of these studies may be important for clinicians in making decisions about the treatment of patients with COVID-19-related ARDS. These studies are listed in Appendix A, http://links.lww.com/EJAIC/A98. We did not submit this addition to amend the PROSPERO registration, because it does not affect core elements of the study.

Results

Study selection

We screened 16 026 titles/abstracts of which 15 907 were excluded (14 985 records that were considered irrelevant to the study objectives and 922 duplicates (Fig. 1)]. Out of the remaining 119 full-text records, we excluded 30 ongoing trials, 19 noninterventional studies and 27 studies with irrelevant study design.

The risk of bias assessment was conducted on the remaining 42 studies (Supplementary Table S1, http://links.lww.com/EJAIC/A99). Of these, eight were excluded because they did not provide the necessary raw data for evaluating the predefined primary and secondary outcomes.[23–30] Furthermore, 21 additional studies were excluded because of a high or critical risk of bias.[63–65] The most frequent critical issue identified in these excluded studies was the lack of a uniform intervention applied to all patients[16–18,28,31–42,55,57,67] (Fig. 1, Table 2).

Twelve studies with a low and moderate bias were included in the primary analysis.[43–46,46–54] All these studies were in-patient control studies, except for one, which was a retrospective case–control study.[48] There were no randomised controlled trials that compared different PEEP interventions. Each study contributed data relevant to only one of the three key questions predefined in our review, specifically addressing the impact of lower vs. higher PEEP levels on various outcome parameters. Most studies primarily focused on variables identified as secondary outcomes, such as gas exchange and respiratory mechanics. Only one study established a correlation between the primary outcomes and the intervention.[48]

Given these limitations, none of the studies reached a level of high-quality evidence. Additionally, the interventions and patient populations included were quite heterogeneous, complicating the feasibility of a meta-analysis. However, because of the absence of high-quality evidence, we opted to provide a descriptive overview of these studies. This approach aims to present the best quality data currently available on PEEP in COVID-19 ARDS. The results of the included studies were presented separately according to the predefined objectives.

Fig. 1 Schematic representation of literature selection process.

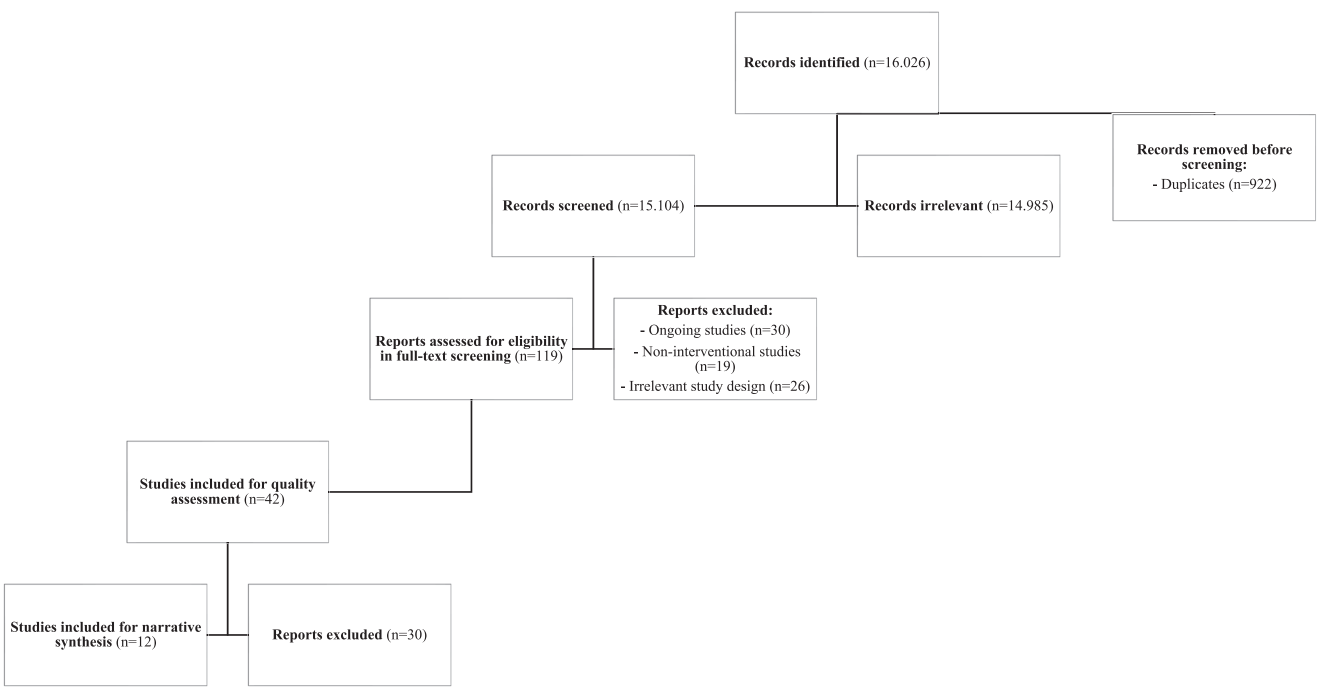


Table 1 **Characteristics of studies included after RoB assessment**

Study	Number of patients	ARDS at inclusion	Study inclusion	PEEP (cmH_2O)	
				Intervention	Control
Grieco, 2020[43]	30	Moderate to severe	24 h p.i.	15	5
Sang, 2020[44]	20	Severe	14 days after beg. of sympt.	15	5
Coppola, 2020[45]	23	Moderate	48 h post ICU adm.	15	5
Ball, 2021[46]	42	Moderate	9 days p.i.	16	8
Chiumello, 2020[47]	32	Mild to severe	72 h post ICU adm.	15	5
Pan, 2021[54]	20	Mild to severe	11 days of MV	10,15	5
Valk, 2021[48]	933/468	Mild to severe	N/A	High PEEP table	Low PEEP table
Chiumello, 2021[49]	61	Moderate to severe	6 days between onset of symptoms and hospital admission	15	5
Jonkmann, 2023[50]	108	Moderate to severe		24 (in 4 patients 16 to 0 cmH_2O)	6
Taenaka, 2023[51]	43	Mild to severe	Within 24 h after ICU admission/24 h postintubation	15	5
Filippini, 2022[52]	99	Mild to severe	Within 5 days after ICU admission	20	10
Grieco, 2023[53]	20	Moderate to severe	Within 24 h after intubation	15	5

ARDS, acute respiratory distress syndrome; beg. of sympt., beginning of symptoms; ICU, intensive care unit; MV, mechanical ventilation; N/A, not available; p.i., post intubation; PEEP, positive end-expiratory pressure; post ICU adm., after the admission to the intensive care unit; RoB, risk of bias.

Objective 1: higher vs. lower positive end-expiratory pressure

One thousand four hundred and thirty-one patients ($n = 20$ to 933) participated in the 12 included studies, which compared lower and higher PEEP levels (Table 1). The severity of ARDS is shown in Table 1. Lower PEEP was set at 5 cmH_2O ($n = 9$),[43–45,47,49,51,53,54] 6 cmH_2O ($n = 3$),[50] 8 cmH_2O ($n = 1$)[46] and 10 cmH_2O ($n = 1$)[52] and higher PEEP at 15 cmH_2O ($n = 9$),[43–45,47,49,51,53,54] 16 cmH_2O ($n = 1$),[46] 20 cmH_2O ($n = 2$),[52] respectively. One study retrospectively classified patients' PEEP settings according to the high or low PEEP/FiO_2 table.[48] In most studies, patients received lung protective ventilation and were deeply sedated and, in several studies, also received myorelaxation (Supplementary Table S3, http://links.lww.com/EJAIC/A101).

PEEP trial protocols varied, using either stepwise PEEP reduction after initial recruitment maneuvers,[43,44,53,54] incremental recruitment manoeuvres from lower to higher PEEP,[45,47] or incremental–decremental PEEP trials[50] (Supplementary Table S3, http://links.lww.com/EJAIC/A101).

Due to the heterogeneity of the study population and differences in the presentation of the data, we were unable to conduct a formal meta-analysis for any of our predefined primary as well as secondary outcomes. Hence, this is a narrative review presentation. The most relevant parameters are summarised in Fig. 2, Table 1, Supplementary Table S2, http://links.lww.com/EJAIC/A100, and Supplementary Table S3, http://links.lww.com/EJAIC/A101.

Primary outcomes

Almost none of our predefined primary outcome parameters was reported by any of the 11 included studies. Only one study reported higher PEEP to be associated with a lower median number of ventilator-free days (as a surrogate of our primary outcome parameter clinical status) (0 vs. 6 days) and a higher incidence of acute kidney injury. No effect on mortality was found[43,48,50] (Supplementary Table S2, http://links.lww.com/EJAIC/A100).

In two studies, a subgroup analysis according to recruitability potential was performed. Recruiters required longer ventilation until successful extubation[52] and length of ICU stay was found to be longer in high recruiters compared with low recruiters.[51]

Secondary outcomes

Overall, four studies presented evidence for improved oxygenation with high PEEP.[43,45,47,49,51,53,50] Two studies found no evidence of negative effects of high PEEP on respiratory system compliance[43,47] or dead space ventilation,[43] whereas the other two reported considerable impairment in respiratory mechanics.[45,49,53,50] One study reported that response to high PEEP varied widely among patients.[49] Three studies found no improvement in oxygenation under ventilation with higher PEEP.[44,46,48] In these studies, higher PEEP was associated with worsened carbon dioxide elimination[44] and higher peak pressures.[48]

Several studies compared the response to higher PEEP according to the recruitability potential of the patients. Two studies underlined a positive effect of higher PEEP levels on oxygenation in patients with high vs. low recruitability potential.[51] The impairment in compliance at higher PEEP levels was only observed in patients with lower recruitability.[51,50] Studies showed that high PEEP improves lung aeration in EIT and chest CT, reducing dorsal silent spaces in high recruiters, especially in the supine position. In low recruiters, high PEEP increases ventral silent spaces regardless of position.[51] Another study found that recruiters showed a greater decrease in nonaerated lung mass from standardised recruitment manoeuvres ($P = 0.024$).[52]

Table 2 **Characteristics of studies excluded after RoB assessment**

Study	Number of patients	ARDS at inclusion	Study inclusion	PEEP (cmH_2O) Intervention	Control
Barthelemy, 2021[31]	30	Moderate	6 days	5-8-10-12-15-18	8
Beloncle, 2020[63]	25	Moderate	26 h p.i. (d1/5)	15	5
Bonny, 2020[55]	10	ARDS	48 h p.i.	16	8
Diehl, 2020[61]	22	Moderate	1 day p.i.	11 mbar	16 mbar
Mauri, 2020[57]	10	Mild to severe	5 days p.i.	15	5
Mezidi, 2020[32]	15	Moderate to severe	N/A	Decrem. PEEP trial 20-6 in obese	Decrem. PEEP trial 20-6 in nonobese
Roesthuis, 2020[29]	14	Mild to moderate	2, 6 days of MV	8-10-12-14-16-18	8
Tsolaki, 2020[33]	17	Moderate to severe	2–3 days of MV	~16	~11
Mittermaier, 2020[34]	15	Mild to moderate	2–60 h p.i.	Decrem. PEEP trial	PEEP table
Sella, 2020[17]	15	hARF	12 days of MV	Best PEEP assessed by EIT	PEEP tables
van der Zee, 2020[18]	15	Moderate to severe	2.26 days of MV (mean) (0 to 8 days)	Best PEEP assessed by EIT	High/low PEEP tables
Morais, 2021[28]	10	Moderate	7d p.i.	Decrem. PEEP trial in supine position	Decrem. PEEP trial in prone position
Depta, 2022[27]	53	Moderate to severe	12 h to 5 days post adm.	Increm. PEEP trial (0-5-8-10-12-15-18) in prone position	Increm. PEEP trial (0-5-8-10-12-15-18) in supine position
Smit, 2021[67]	27	Moderate to severe	Early CT - directly p.i. Late CT to 12.5 days p.i.	20	Low PEEP/FiO2 table
Protti, 2021[35]	40	Mild to severe	3 days p.i.	10, 15, CT scan at Ppeak 45 cmH_2O	5, CT scan at Ppeak 15 cmH_2O
Oller Sanchez, 2021 (abstract)	15	Mild to severe	1 h p.i.	Optimal PEEP by EXPRESS PEEP protocol, positive oesophageal pressure	optPEEP by EXPRESS PEEP, negative oesophageal pressure
Gibot, 2021[16]	17	Moderate to severe	N/A	High PEEP table	Low PEEP table
Ottolina, 2022[36]	101	Moderate to severe	N/A	High (14.7 cmH_2O)/ medium PEEP (12 cmH_2O)	Low PEEP (9.6 cmH_2O)
Yaroshetskiy, 2022[38]	116	ARDS	N/A	10, 12, 14	8
Zerbib, 2022[37]	30	Moderate to severe	N/A	Post-LRM	Pre-LRM
Dell Anna, 2022[39]	9	Moderate to severe	2 (1 to 3) days of MV	15/PEEP to obtain Ppleau <28 cmH_2O	5
Mojoli, 2023[40]	38	Moderate to severe	N/A	Clinical PEEP+6 cmH_2O	Clinical PEEP 6 cmH_2O
Petenuzzo, 2022	36	Mild to moderate	9 (4 to 11) days after symptoms onset, 1 (1 to 2) days postintubation	20	8
Scaramuzzo, 2023	17	Moderate to severe	N/A	High PEEP (15 $\pm$ 5 cmH_2O), intermediate PEEP (10.6 $\pm$ 3.8 cmH_2O)	Low PEEP (5.6 $\pm$ 2.2 cmH_2O)
Somhorst, 2022[41]	75	Moderate to severe	3 days (1 to 8) post intubation	EIT-set PEEP (PEEP set)	PEEP according to high PEEP-FiO_2 table (PEEP base)
Tsolaki, 2023[42]	106	Severe	Within 48 h after ICU admission, two groups: 'early intubation' and 'late intubation' (more than 21.5 h)	PEEP decrease by 30%	PEEP 2 cmH_2O lower than suggested by SSC
Nakayama, 2023	33	Mild to severe	0 [0 to 1] of MV	15	5
Gillmann, 2022[65]	40	Moderate to severe	2 (1 to 11) d of MV	15	5
da Cruz, 2024[25]	184	Moderate to severe	MV<=48 h	20	6
Marrazzo, 2023[24]	12	Mild to moderate	3 ($\pm$2 days) after the intubation, 12 ($\pm$5) from symptoms onset	25	6

ARDS, acute respiratory distress syndrome; CT, computed tomography; Decrem. PEEP trial, decremental PEEP trial; EIT, electrical impedance tomography; Increm. PEEP, incremental PEEP trial; LRM, lung recruitment; MV, mechanical ventilation; N/A, not available; p.i., post intubation; PEEP, positive end-expiratory pressure; post adm., after the admission; RoB, risk of bias.

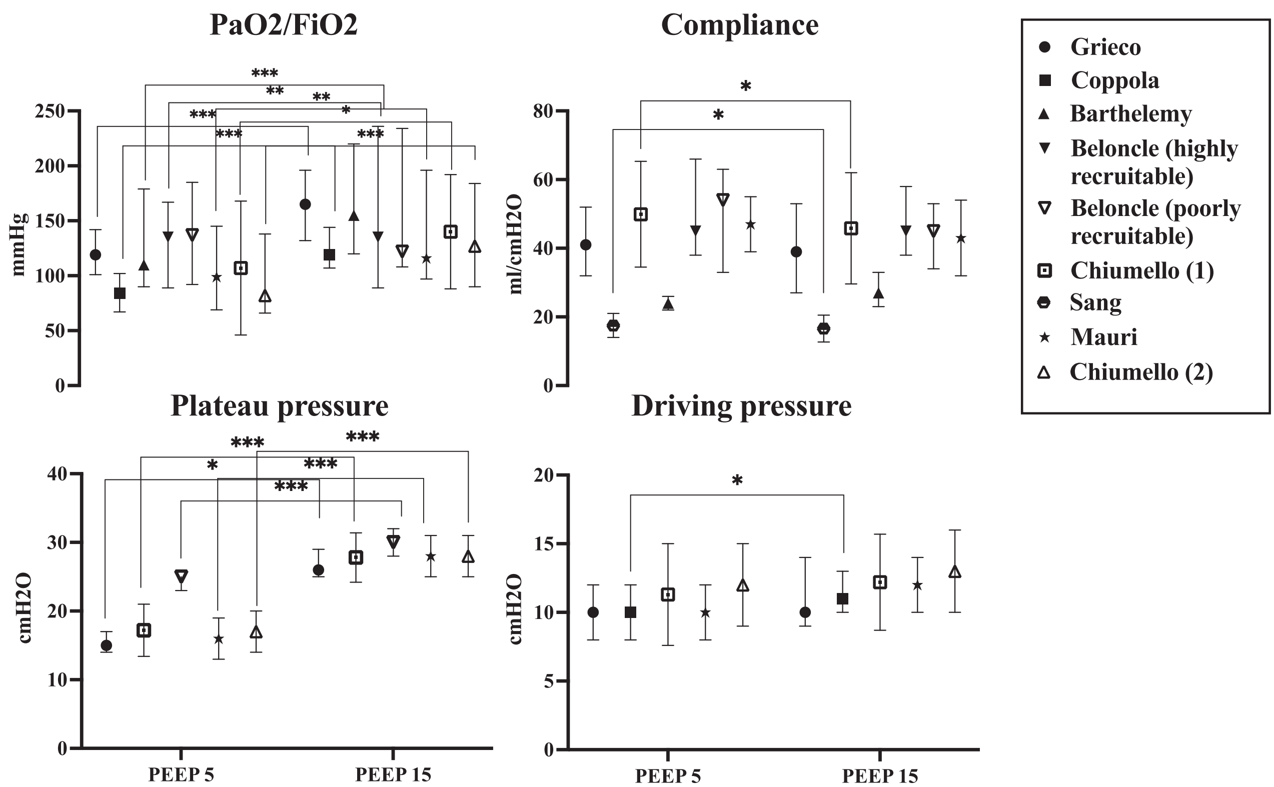
Objective 2: individualised positive end-expiratory pressure vs. standardised positive end-expiratory pressure

We identified no studies that would compare ventilation with individually determined PEEP with ventilation with PEEP set according to standardised approaches (low-ARDS and high-ARDS network PEEP tables).

Objective 3: individualised positive end-expiratory pressure determination

Although none of the studies reviewed directly compared standardised vs. individualised PEEP determination methods, many assessed the optimal PEEP level and its impact on gas exchange and lung mechanics Fig. 3. In this section, we made an exception and reviewed all studies

Fig. 2 Gas exchange and lung mechanics under high and low positive end-expiratory pressure.



Box plots on gas exchange (P_aO_2/FiO_2) and lung mechanics at low (5 cmH_2O) and high 15 cmH_2O PEEP levels in selected studies. Most studies are shown with median and interquartile range. In the study by Mauri (compliance, driving pressure) mean and standard deviation were used. PEEP, positive end-expiratory pressure. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

included in the full-text screening independently of their risk of bias because these studies provided valuable examples of PEEP titration methods that we believe to be important to present to the scientific community.

Studies varied in optimal PEEP titration methods, including EIT,[16,17,24,26,50,55] transpulmonary pressure measurement,[34,18] PEEP trials targeting optimal gas exchange,[34,38] respiratory mechanics[54,56] or ventilator-based variables.[25,27]

Best positive end-expiratory pressure by electrical impedance tomography

EIT monitoring in 12 studies showed heterogeneous results,[16–18,24–26,28,41,51,50,55,57] with optimal PEEP ranging from 10 to 21 cmH_2O.[17,55] Some studies found EIT-based best PEEP within high and low PEEP recommendations,[16,17] whereas others reported no significant difference from high-PEEP table values.[41] Optimal PEEP varied by recruitment potential,[50] improving pulmonary compliance and ventilation distribution compared to high-PEEP table recommendations,[16] and was influenced by body position, being lower in semi-recumbent than supine positions.[24]

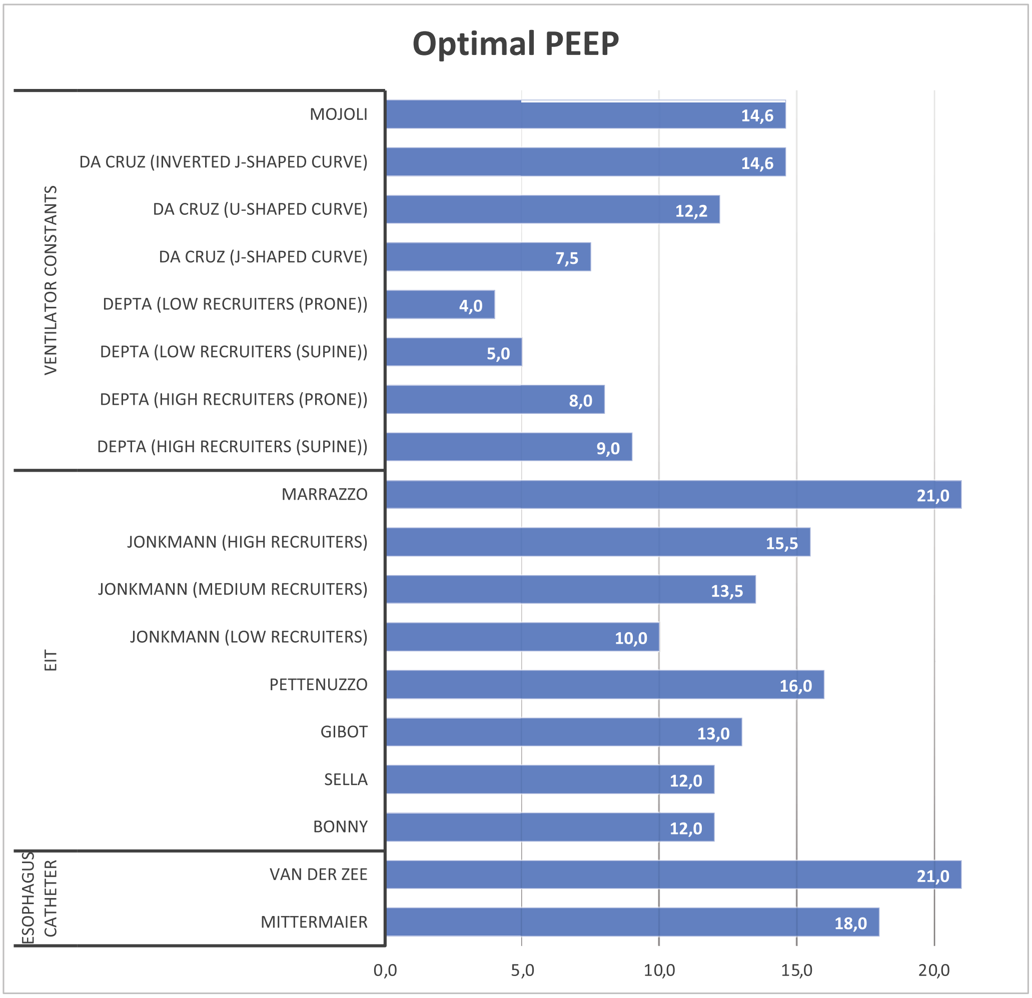
Best positive end-expiratory pressure by oesophageal pressure monitoring

Eleven studies used oesophageal pressure monitoring to evaluate the ventilation in C-ARDS patients.[16,18,24,28,30,32,34,37,38,45,55] When comparing ventilation at a PEEP leading to negative transpulmonary end-expiratory pressure and PEEP associated with positive transpulmonary end-expiratory pressure, the former was associated with lower compliance, higher driving pressure and less improvement in oxygenation as compared with the latter.[30] In another study, the optimal PEEP level determined by the oesophageal catheter was greater than 10 cmH_2O in nonobese and greater than 16 cmH_2O in obese patients.[32]

Ventilator-derived best positive end-expiratory pressure

One study categorised C-ARDS patients by ventilator-derived measured expiratory time constant (TauE), identifying recruitable (75%) and nonrecruitable (25%) groups, and found no difference in mean optimal PEEP between TauE and compliance-based methods.[56] In a study, C-ARDS patients were classified by dPaw-vs.-PEEP curves (J-shaped, inverted-J or U-shaped), revealing varied optimal PEEP levels to minimize driving

Fig. 3 Optimal positive end-expiratory pressure level determined in reviewed studies.



Methods of optimal PEEP titration: Mojoli: hysteresis-based best PEEP. Da Cruz – best PEEP based on dPaw-vs.-PEEP curves. Depta – best PEEP based on TauE (measured expiratory time constant). The highest TauE represented the best tradeoff between recruitment and overdistention. Marazzo – PEEP associated with the best compromise between overdistension and collapse in EIT. Jonkmann – optimal EIT-based PEEP was first defined as the crossing point of the collapse and overdistension curves during decremental PEEP trial. Petenuzzo – PEEP at the intersection between curves representing the cumulative percentage of compliance loss due to either collapse or overdistension. Gibot – PEEP associated with the best compromise between overdistension and collapse in EIT. Sella – best PEEP was determined according to the lowest relative alveolar collapse and overdistension in EIT. PEEPeit was different from ARDSnet low [9 (8 to 10) cmH_2O] and high [17 (16 to 20) cmH_2O] PEEP tables. Bonny – best PEEP was determined according to the lowest relative alveolar collapse and overdistension in EIT. van der Zee – best PEEP was set above the intersection of the curves representing relative alveolar overdistension and collapse in EIT. PEEPeit was different from ARDSnet low (11 cmH_2O) and high (19 cmH_2O) PEEP tables. Mittermaier – best PEEP was determined by a decremental PEEP trial according to the best P_aO_2/FiO_2 index.

pressure, with about 90% needing below 12 cmH_2O and only 10% requiring over 15 cmH_2O, correlating with curve shape and BMI.[25] A study comparing best PEEP determined by tidal lung hysteresis and best compliance PEEP found three patterns of tidal recruitment, recommending adjustments in PEEP levels based on recruitment potential, with hysteresis-based PEEP averaging 14.6 cmH_2O, which differed from best compliance PEEP, especially in high and biphasic recruiters.[40]

Best positive end-expiratory pressure according to positive end-expiratory pressure trial

One study aligned the best PEEP level closely with high-PEEP table recommendations (17.9 and 16 mbar, respectively),[34] whereas another suggested that PEEP levels above 10 cmH_2O could cause lung overdistension, identifying 11 cmH_2O as optimal and noting low recruitment potential at any timepoint.[38] Comparatively, a study found that best compliance PEEP was the lowest and resulted in reduced plateau pressure, driving pressure and mechanical power, challenging the efficacy of high PEEP or oxygenation-based adjustments.[54]

Discussion

We assessed the evidence on PEEP settings in COVID-19 patients and included 12 prospective and retrospective cohort studies with more than 1431 patients in our main analysis.[43–46,46–54] Overall, for our main questions, we were unable to provide high-quality evidence in favour of both predefined interventions (higher vs. lower PEEP or individualised PEEP vs. standardised PEEP). The data was not suitable for a structured meta-analysis because of the heterogeneity of populations (early vs. late admission after initiation of mechanical ventilation) and heterogeneity in the reported outcome parameters.

Concerning objective 1, which compared the effect of higher vs. lower PEEP, the following conclusions could be made:

(1) Regarding outcomes, we identified four groups of studies, showing
  (a) improvement in oxygenation, but worsening of lung mechanics with higher PEEP conditions
  (b) little or no effect on gas exchange but worsening of lung mechanics
  (c) improvement in gas exchange without effect on lung mechanics
  (d) improvement in gas exchange and haemodynamics according to the recruitability potential of a patient
(2) High PEEP may negatively affect the outcome and result in a higher incidence of acute kidney injury.
(3) There was a large heterogeneity in the response to PEEP in C-ARDS patients' response to PEEP and the response may depend on the recruitability potential of a patient.
  We did not identify any studies which would address the objective 2 (individualised vs. standardised PEEP). Concerning objective 3 (individualised PEEP determination), we can summarise the existing data as follows:
(1) PEEP titration methods are variable. The most commonly used methods are PEEP trial driven either by optimization of gas exchange or respiratory mechanics, EIT, lung CT and ventilator-based titration methods.
(2) Individual best PEEP values vary, ranging from 5 to 21 cmH_2O.

Concordant with the evidence on mixed non-COVID-19 ARDS population,[6,7] data on PEEP settings in COVID-19 ARDS is limited and quite heterogeneous. Thus, even in this context, while the positive effect on oxygenation is emphasised,[7] there is no definitive conclusion on the impact of PEEP on mortality as the primary outcome. The latest meta-analysis indicates some survival benefit of higher PEEP in moderate-to-severe ARDS, while it also highlights the significant clinical heterogeneity, attributable to the high variability in patient cohorts and PEEP titration methods – a pattern also observed in case of COVID-19-associated ARDS.[6]

High PEEP improves oxygenation in COVID-19 pneumonia,[58] as shown in eight studies with low-to-moderate risk[43,45,47,49–53] of bias, reporting better early-ventilation phase oxygenation at higher PEEP. Despite potential benefits like lung reaeration and shunt reduction, high PEEP is also associated with adverse effects such as barotrauma,[59] decreased compliance,[23,35,49,53,56,60] shear trauma,[60] increased dead space ventilation[4,29,46,57,61] and hemodynamic consequences, including a higher incidence of acute kidney injury in some studies.[31,36,42,48,55,] These findings underscore the complex balance between high-PEEP oxygenation benefits and its risks,[31,35,45] particularly emphasising that only patients with high recruitment potential may experience positive effects.[25,50–52]

During the COVID-19 pandemic's onset, Gattinoni *et al.*[62] identified two phenotypes: the 'L' type with low elastance and high compliance, and the later 'H' type with high elastance. Studies also categorised patients as 'recruiters' and 'nonrecruiters' regarding high PEEP ventilation's benefits, though these categories and their proportions varied significantly across studies.[35,37,49,53,63] Variations in disease stages, patient enrolment times and recruitment definitions[44,46,57,63] – complicated the ability to draw broad conclusions.

The heterogeneity of C-ARDS suggests that ventilation strategies may only apply to specific subgroups. The ARDS Network PEEP table fails to account for varied causes and patient phenotypes, implying a one-size-fits-all approach to different forms of severe respiratory distress.[66]

Several methods exist for determining optimal PEEP in ARDS patients. These include recruitment CT,[5,46,67] EIT with its noninvasive nature and ability to differentiate between unventilated, ventilated and hyperinflated lung areas,[17,18,63] and incremental–decremental PEEP trials for their simplicity and dynamic assessment, despite varied protocols.[18,29,32,55] Transpulmonary pressure measurement offers another advanced method.[68,69] This diversity, along with varying diagnostic approaches and the absence of systematic control using ARDS PEEP tables, contributes to the significant variability in study outcomes.

Despite a considerable number of studies investigating ventilation strategies in C-ARDS, none provide sufficient quality for evidence-based strategies guiding PEEP settings in this etiologically defined ARDS. Although there are potential benefits of individualised PEEP (which were, unfortunately, not systematically reported in the reviewed studies), the individualised approach could be challenging, especially under pandemic conditions, because of the time-consuming and resource-consuming methods, lack of experience with technically challenging approaches (such as EIT and oesophageal pressure measurement) or limited financial resources. However, if future studies show significant benefits of individualised approaches that lead to better outcomes in these critically ill patient groups, thereby reducing the burden on the healthcare system, the investment in the further dissemination of these technologies could potentially outweigh their cost or human resource requirements.

Conclusion

In C-ARDS optimal strategies to determine PEEP levels and their effects on primary endpoints such as mortality remain elusive because of a lack of well designed studies. The few available trials of sufficient quality address only secondary, clinically less important endpoints (e.g. short-term changes in gas exchange and lung mechanics). Currently, we cannot derive evidence-based recommendations on optimal PEEP levels or methods of its determination in C-ARDS. There is an urgent need for novel, precisely designed or adaptive trials, comparing different PEEP levels or PEEP titration methods. These studies should also consider different ARDS causes and its application with respect to the time course of the disease or concentrate on a single ARDS entity so that the results can identify the sources of the clinical heterogeneity identified by previous research and determine therapeutic schemes for different disease subgroups.

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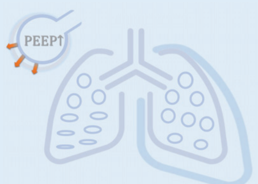
VISUAL ABSTRACT

The determination of „Best-PEEP“ in the ventilation strategy of critically ill Covid-19 patients - a systematic review

OBJECTIVES

For patients with COVID-19 associated ARDS

1) Does an **individual PEEP-assessment** lead to different PEEP settings compared to **standard approaches**?
2) What are the effects of **individualized PEEP levels** compared to **standard approaches**?
3) What are the effects of the treatment strategy with **lower PEEP** settings compared to treatment strategies with **higher PEEP** settings?



METHOD: SYSTEMATIC REVIEW

- LITERATURE SEARCH – 16026 studies
- SCREENING – 42 studies **included**
- RISK OF BIAS ASSESSMENT – 30 studies **excluded**
- NARRATIVE SYNTHESIS – 12 studies **included**

RESULTS and CONLUSION

- **Meta-analysis** not possible
- **Heterogenous results**
- **12 cohort studies** comparing the effects of high vs. low PEEP
- **High PEEP** levels may **improve oxygenation**, but lead to worsening of **lung mechanics**, **prolonged mechanical ventilation**, and an increased rate of **renal failure**.
- **Optimal PEEP** range between 5 and 21 cmH2O

! Evidence regarding the **optimal PEEP in COVID-19-ARDS** or the way to determine it was inconclusive.

i **PEEP:** Positive end-expiratory pressure

i **ARDS:** Acute respiratory distress syndrome