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# Methods for determination of optimal positive end-expiratory pressure: a protocol for a scoping review

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## ABSTRACT

**Introduction** Titrated application of positive end-expiratory pressure (PEEP) is an important part of any mechanical ventilation strategy. However, the method by which the optimal PEEP is determined and titrated varies widely. Methods for determining optimal PEEP have been assessed using a variety of different study designs and patient populations. We will conduct a scoping review to systematically identify all methods for determining optimal PEEP, and to identify the patient populations, outcomes measured and study designs used for each method. The goal will be to identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to further systematically synthesise and meta-analyse existing literature.

**Methods and analysis** Using scoping review methodology, we will generate a comprehensive search strategy based on inclusion and exclusion criteria generated using the population, concept, context framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of Science and Scopus). Three investigators will independently screen titles and abstracts, and two investigators will independently complete full-text review and data extraction. Included citations will be categorised in terms of PEEP method, study design, patient population and outcomes measured. The methods for PEEP titration will be described in detail, including strengths and limitations.

**Ethics and dissemination** Given this is a synthesis of existing literature, ethics approval is not required. The results will be disseminated to stakeholders via presentation at local, regional and national levels, as well as publication in a high-impact critical care journal. There is also the potential to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by societies.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will rigorously describe studies testing methods of determining optimal positive end-expiratory pressure. Each method will be summarised with a description, its strengths and limitations.
⇒ Inclusion of many different study designs, not just randomised control trials will allow for identification of methods that are well studied or those that could be better studied.
⇒ A potential limitation is that given the broad nature of the review, there will be a large volume of studies to synthesise, and this may be challenging to summarise in one review.

## INTRODUCTION

Titrated application of positive end-expiratory pressure (PEEP) during mechanical ventilation is a crucial part of any ventilatory strategy. PEEP can be beneficial in several ways. PEEP increases mean airway pressure which can improve oxygenation by recruiting collapsed alveoli and reducing intrapulmonary shunt.[1] PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimising atelectrauma.[2] However, excessive PEEP can also have detrimental impacts through its effects on the respiratory and cardiac systems. Overdistension of the lungs from high PEEP can lead to VILI via barotrauma.[2] Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output.[2] Several methods exist to determine the best or optimal PEEP to apply during mechanical ventilation, but significant variability exists in terms of which methods are used by clinicians.

Several large randomised controlled trials (RCTs) have assessed different methods for selecting the best PEEP in patients with acute respiratory distress syndrome (ARDS). The ALVEOLI study randomised patients with ARDS to either low or high PEEP methods based on prespecified tables that titrated PEEP higher as the fraction of inspired oxygen ($FiO_2$) increased.[3] The investigators found no differences in terms of mortality or discharge home without ventilatory support.[3] The EXPRESS trial randomised patients with ARDS to a low PEEP method of 5–9 $cmH_2O$ versus a method that maximised PEEP while maintaining a plateau

pressure between 28 and 30 $cmH_2O$.[4] There was no difference in mortality or hospital discharge.[4] The Lung Open Ventilation Strategy (LOVS) trial randomised patients to a method of lower PEEP while maintaining plateau pressures under 30 $cmH_2O$ versus an open lung method involving recruitment manoeuvres and high PEEP while maintaining plateau pressures under 40 $cmH_2O$.[5] Again, no difference in mortality or duration of mechanical ventilation was demonstrated.[5] Many other methods of PEEP titration have been described, however, these have not been rigorously tested through RCTs or been studied in terms of their impact on clinical outcomes.[6] Clinical practice guidelines regarding ventilator management in ARDS suggest higher PEEP may be beneficial in patients with moderate-to-severe ARDS but acknowledge the optimal method for PEEP titration is not yet clear.[7]

Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance,[8] driving pressure[9] and transpulmonary pressure.[10] Furthermore, a range of techniques are described to achieve these targets, such as the use of oesophageal balloons,[10] stress index[11] or pressure-volume curves.[12] Lastly, the largest studies examining PEEP were conducted in ARDS patients, but the external validity to other populations, such as those with normal lungs or acute hypoxaemic respiratory failure without ARDS remains unclear. Previous systematic reviews have focused only on RCTs, thus excluding many studies examining alternative PEEP titration methods and physiological titration targets.[13–17] To date, there has not been a comprehensive review that has synthesised all known PEEP titration methods, regardless of patient population or study design.

Scoping reviews are a form of knowledge synthesis that systematically search, select and synthesise knowledge around a research question that aims to describe key concepts, types of evidence and identify gaps in the literature.[18] The aims of this study are to use scoping review methodology to describe the methods of PEEP titration that have previously been studied, describe the patient populations they have been studied in, characterise the various clinical outcomes and endpoints used, as well as describe the different study designs used. The results of the review will identify knowledge gaps for future research in this area. For example, it will serve to identify the methods that are currently well studied as well as other methods that show promise but are lacking in high quality evidence such as randomised trials. Furthermore, this review could serve as the foundation for future point prevalence studies or surveys that aim to map real-world utilisation of various methods. It may also be used to inform policy and procedures within individual sites and could be used as a resource in the development of clinical practice guidelines.

## METHODS AND ANALYSIS

### Conceptual model

This scoping review was registered using Open Science Framework (https://osf.io/atzqc). Although no Enhancing the Quality and Transparency of Health Research guidance on scoping review protocols exists, this protocol was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol statement and checklist[19] where applicable. The scoping review itself will be prepared in accordance with the framework initially proposed by Arksey and O'Malley[20] with updates from Levac *et al*[21] and most recently updated by the Joanna Briggs Institute.[22] The findings of our research will be reported in accordance with the PRISMA Scoping Review statement and checklist.[23]

### Patient and public involvement

This work describes existing research studies, and thus involves no patients or members of the public.

### Identifying the research question

In identifying a research question for the scoping review, we followed the recommended population, concept, context (PCC) framework.[22]

1. The population of interest involves adults (18 years of age or older) undergoing invasive mechanical ventilation in hospital. Patients with ARDS, acute hypoxaemic respiratory failure and those receiving invasive mechanical ventilation for non-pulmonary indications such as during surgery will be included.
2. The primary concept is to describe methods used in setting or titration of PEEP on the ventilator and the clinical and physiological outcomes associated with these different methods.
   Some examples of PEEP titration methods include (but are not limited to): Using PEEP tables (high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure, pressure-volume curves and inflection points, oesophageal balloons to measure transpulmonary pressure or various imaging modalities (CT or ultrasound or electrical impedance tomography).
   The outcomes associated with the above-mentioned methods will be broad and could include clinical outcomes such as mortality, intensive care unit (ICU) length of stay or duration of mechanical ventilation. Other outcomes may relate to respiratory mechanics and physiology, including FiO2, dead space, compliance or oxygenation.
3. The context will include those patients receiving planned or unplanned invasive mechanical ventilation in the ICU, operating theatre or the emergency department. It will not be limited based on duration of ventilation, geography, culture or gender.

Based on the above considerations, this scoping review will seek to answer the following question:

Table 1 Inclusion and exclusion criteria, developed based on the population, concept, context framework

| | Inclusion | Exclusion |
|---|---|---|
| Population | ► Patients undergoing invasive mechanical ventilation in hospital<br>► Any setting in hospital including intensive care unit, operating room, emergency department) | ► Paediatric and neonatal population<br>► Non-invasive ventilation<br>► Single lung ventilation<br>► Animal studies (with no human component) |
| Concept | ► Study evaluates a method of setting optimal PEEP<br>► Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method | ► Studies that arbitrarily set PEEP at a certain value (ie, 5 $cmH_2O$) |
| Context | ► Any geographical location<br>► Any duration of ventilation | ► None |
| Types of Evidence | ► Primary research studies (including randomised controlled trials, cohort studies, cross-sectional studies, case series)<br>► Published abstracts will be included | ► None |

PEEP, positive end-expiratory pressure.

In hospitalised adults undergoing invasive mechanical ventilation, what are the methods for determining optimal positive end-expiratory pressure that currently exist in the literature. For these methods, what patient populations along with clinical and physiological outcomes have been studied, and what study designs have been used to examine their efficacy and/or effectiveness?

The inclusion and exclusion criteria and creation of a search strategy were conducted as previously described for scoping reviews.[22] The development of the criteria was based on the PCC framework and can be seen in table 1.

## Identifying relevant studies

Based on the inclusion and exclusion criteria, literature search strategies were developed by an expert librarian (HLR) for MEDLINE, EMBASE, CENTRAL, Web of Science and Scopus. Articles will be included from inception of databases up until the date of the search. The search strategy draft for all databases can be seen in online supplemental material tables S1–S5. The search strategy was peer-reviewed by another librarian (ZAP) using the Peer Review of Electronic Search Strategies (PRESS) guideline statement.[24] The search results in the different databases will be exported to EndNote V.20 and the screening process will be completed using the systematic review software Rayyan. The initial database search will be conducted early May 2023 and may be updated as needed depending on the duration between initial search and completion of the project.

## Study selection

The workflow for study selection will be presented in a PRISMA flow diagram as well as in narrative form. All titles and abstracts will be screened by at least two reviewers (between KKSP, SE and TS). Prior to completing screening of all titles, we will review 100 random selections to assess inter-rater reliability and if there is a discrepancy, we will further clarify inclusion and exclusion criteria. After title and abstract and screening is complete, disagreements will be resolved via discussion between the three reviewers. After title and abstract screening is completed, the full text of all included manuscripts will be reviewed independently by two reviewers (KKSP and SE) to confirm eligibility. At this stage, the reason for exclusion will be recorded in the PRISMA diagram. In addition to identifying articles through the search strategy, reference lists of included papers will be reviewed to identify any other manuscripts that were not captured with the initial search. For any studies for which the full manuscript is not accessible, an email will be sent to the corresponding author requesting a copy of the manuscript. Manuscripts of another language will be translated to English using Google Translate whenever possible.[25]

## Data extraction

Once included manuscripts are identified, relevant study data will be abstracted using a standardised form. This form aims to collect all relevant variables of interest and was developed over several iterations with input from all members of the team. It is based on a template suggested by the Joanna Briggs Institute.[26] The key variables that will be extracted are summarised in table 2. Two reviewers (SE and KKSP) will independently extract data from 5 to 10 studies to assess consistency and to pilot test whether the form needs to be adjusted to capture all the relevant data. Once data extraction has started, iterative refinement of the data abstraction form may be made to tailor to the data abstracted. Abstracted data will be collated in a Microsoft Excel spreadsheet.

## Presentation of results

Extracted data will be reported by using several different data displays. All included studies will be aggregated in a table summarising key study characteristics. This will include the setting, the study design, country of origin,

Table 2 Data to be abstracted from eligible studies included in the scoping review

| Domain | Categories |
|---|---|
| Study identifiers | First author, journal, year of publication, country of publication, publication type |
| Study design | Study type or design, multicentre versus single centre, country/countries of participants, funding source |
| Participants | No of participants, patient population, underlying disease severity, study setting |
| Results | Method (s) of selecting PEEP, comparator, tidal volumes within experimental and control groups |
| Outcomes | Clinical outcomes could include mortality, length of stay, ventilation outcomes or others. Respiratory or physiological outcomes could include P/F ratio, oxygenation, compliance, plateau pressure, driving pressure or others. |

PEEP, positive end-expiratory pressure; P/F, Partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen .

time period, patient population, the method of PEEP selection and the outcomes measured.

Based on the number of studies within each setting and method of selection, we will stratify the data for those with adequate number of studies. Data will be presented in terms of setting, patient population and number of participants, study design (with focus on RCTs), outcomes (with focus on clinical outcomes), trend over time in publishing, countries involved and most common publishing journals. A table will also describe all RCTs in detail.

The methods for titrating PEEP will be presented in a table that describes how they were performed, as well as benefits and limitations of each method. In addition, methods that have insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the literature and opportunities for future research will be highlighted.

## ETHICS AND DISSEMINATION

As this study will identify and review previously published literature, no research ethics board approval is required.

### Implications

Given the rapidly growing body of evidence concerning methods of determining optimal PEEP, there is a need to rigorously map the literature. This will be accomplished with this scoping review. The results will be presented at local (departmental grand rounds), regional (Alberta Society of Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada Annual Forum) and will be submitted for publication in a peer-reviewed critical care journal. It is anticipated the study may identify certain methods of setting PEEP that have been studied extensively and warrant further synthesis with systematic review and meta-analysis. The results of this review will need to be interpreted within the limitations of scoping review methodology. These include lack of assessment of quality or risk of bias, and lack of quantitative meta-analysis of outcomes. It will also serve to identify methods with potential benefit but where high-quality randomised trials have not been conducted. This will guide future primary research studies. Clinicians will be able to use this synthesis of studies to inform the development and implementation of an optimal PEEP protocol within their hospital or region. The outputs will be relevant to many stakeholders within the healthcare system, including bedside clinicians (including physicians, nurses and respiratory therapists), managers and team leads (who may be developing ventilator protocols and policies) as well as researchers and policy-makers in the field who are responsible for development of clinical practice guidelines.

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## REFERENCES

1 Mélot C. Contribution of multiple inert gas elimination technique to pulmonary medicine. 5. ventilation-perfusion relationships in acute respiratory failure. *Thorax* 1994;49:1251–8.
2 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2014;370:980.
3 Brower RG, Lanken PN, MacIntyre N, *et al*. Higher versus lower positive end-Expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–36.
4 Mercat A, Richard J-C, Vielle B, *et al*. Positive end-Expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646–55.
5 Meade MO, Cook DJ, Guyatt GH, *et al*. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-Expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637–45.
6 Millington SJ, Cardinal P, Brochard L. Setting and titrating positive end-Expiratory pressure. *Chest* 2022;161:1566–75.
7 Fan E, Del Sorbo L, Goligher EC, *et al*. An official American Thoracic society/European society of intensive care medicine/society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1253–63.
8 Pintado M-C, de Pablo R, Trascasa M, *et al*. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respir Care* 2013;58:1416–23.
9 Amato MBP, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–55.
10 Talmor D, Sarge T, Malhotra A, *et al*. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359:2095–104.
11 Chiumello D, Cressoni M, Carlesso E, *et al*. Bedside selection of positive end-Expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Crit Care Med* 2014;42:252–64.
12 Amato MB, Barbas CS, Medeiros DM, *et al*. Beneficial effects of the "open lung approach" with low Distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1835–46.
13 Dianti J, Tisminetzky M, Ferreyro BL, *et al*. 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. *Am J Respir Crit Care Med* 2022;205:1300–10.
14 Briel M, Meade M, Mercat A, *et al*. 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;303:865–73.
15 Dasenbrook EC, Needham DM, Brower RG, *et al*. Higher PEEP in patients with acute lung injury: a systematic review and meta-analysis. *Respir Care* 2011;56:568–75.
16 Sud S, Friedrich JO, Adhikari NKJ, *et al*. Comparative effectiveness of protective ventilation strategies for moderate and severe acute respiratory distress syndrome. A network meta-analysis. *Am J Respir Crit Care Med* 2021;203:1366–77.
17 Walkey AJ, Del Sorbo L, Hodgson CL, *et al*. Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S297–303.
18 Amog K, Pham B, Courvoisier M, *et al*. The web-based "right review" tool asks reviewers simple questions to suggest methods from 41 knowledge synthesis methods. *J Clin Epidemiol* 2022;147:42–51.
19 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
20 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int. J. Soc. Res. Methodol 2005;8:19–32.
21 Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69.
22 Peters MDJ, Marnie C, Tricco AC, *et al*. Updated methodological guidance for the conduct of Scoping reviews. *JBI Evid Synth* 2020;18:2119–26.
23 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for Scoping reviews (PRISMA-SCR): checklist and explanation. *Ann Intern Med* 2018;169:467–73.
24 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40–6.
25 Jackson JL, Kuriyama A, Anton A, *et al*. The accuracy of Google translate for abstracting data from non-English-language trials for systematic reviews. *Ann Intern Med* 2019;171:677–9.
26 Peters MDJ, Godfrey CM, McInerney P, *et al*. Chapter 11: Scoping reviews. In: Aromataris E, Munn Z, eds. *JBI Manual for Evidence Synthesis*. Adelaide: JBI, 2020.