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REVIEW ARTICLE/BRIEF REVIEW

Methods for determining optimal positive end-expiratory pressure in patients undergoing invasive mechanical ventilation: a scoping review

Méthodes de détermination de la pression expiratoire positive optimale chez la patientèle sous ventilation mécanique invasive : une étude de portée

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Abstract

Purpose *There is significant variability in the application of positive end-expiratory pressure (PEEP) in patients undergoing invasive mechanical ventilation. There are numerous studies assessing methods of determining optimal PEEP, but many methods, patient populations, and study settings lack high-quality evidence. Guidelines make no recommendations about the use of a specific method because of equipoise and lack of high-quality evidence. We conducted a scoping review to determine which methods of determining optimal PEEP have been studied and what gaps exist in the literature.*

Source *We searched five databases for primary research reports studying methods of determining optimal PEEP among adults undergoing invasive mechanical ventilation. Data abstracted consisted of the titration method, setting, study design, population, and outcomes.*

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Principle findings *Two hundred and seventy-one studies with 17,205 patients met the inclusion criteria, including 73 randomized controlled trials (RCTs) with 10,733 patients. We identified 22 methods. Eleven were studied with an RCT. Studies enrolled participants within an intensive care unit (ICU) (216/271, 80%) or operating room (55/271, 20%). Most ICU studies enrolled patients with acute respiratory distress syndrome (162/216, 75%). The three most studied methods were compliance (73 studies, 29 RCTs), imaging-based methods (65 studies, 11 RCTs), and use of PEEP-F_IO_2 tables (52 studies, 20 RCTs). Among ICU RCTs, the most common primary outcomes were mortality or oxygenation. Few RCTs assessed feasibility of different methods (n = 3). The strengths and limitations of each method are discussed.*

Conclusion *Numerous methods of determining optimal PEEP have been evaluated; however, notable gaps remain in the evidence supporting their use. These include specific populations (normal lungs, patients weaning from mechanical ventilation) and using alternate outcomes (ventilator-free days and feasibility) and they present significant opportunities for future study.*

Study registration *Open Science Framework (https://osf.io/atzqc); first posted, 19 July 2022.*

Résumé

Objectif *Il existe une variabilité significative dans l'application de la pression expiratoire positive (PEP) chez les personnes sous ventilation mécanique invasive. De nombreuses études évaluent les méthodes permettant de déterminer la PEP optimale, mais de nombreuses méthodes, populations de patient·es et contextes d'étude manquent de données probantes de haute qualité. Les lignes directrices ne font aucune recommandation concernant l'utilisation d'une méthode spécifique en raison du principe d'équivalence et du manque de données probantes de haute qualité. Nous avons réalisé une étude de portée afin de déterminer quelles méthodes de détermination de la PEP optimale ont été étudiées et quelles lacunes existent dans la littérature.*

Sources *Nous avons mené des recherches dans cinq bases de données afin d'en tirer des rapports de recherche primaires étudiant les méthodes de détermination de la PEP optimale chez les adultes sous ventilation mécanique invasive. Les données résumées comprenaient la méthode de titrage, le contexte, la conception de l'étude, la population et les résultats.*

Constatations principales *Deux cent soixante et onze études portant sur 17 205 patient·es répondaient aux critères d'inclusion, dont 73 études randomisées contrôlées (ERC) portant sur 10 733 patient·es. Nous avons identifié 22 méthodes. Onze ont été étudiées dans le cadre d'ERC. Les études ont recruté des participant·es dans une unité de soins intensifs (USI) (216/271, 80 %) ou en salle d'opération (55/271, 20 %). La plupart des études réalisées aux soins intensifs ont recruté des patient·es souffrant d'un syndrome de détresse respiratoire aiguë (162/216, 75 %). Les trois méthodes les plus étudiées étaient l'observance (73 études, 29 ERC), les méthodes basées sur l'imagerie (65 études, 11 ERC) et l'utilisation de tables de PEP-FIO2 (52 études, 20 ERC). Parmi les ERC en soins intensifs, les critères d'évaluation principaux les plus courants étaient la mortalité ou l'oxygénation. Peu d'ERC ont évalué la faisabilité de différentes méthodes (n = 3). Les forces et les limites de chaque méthode sont discutées.*

Conclusion *De nombreuses méthodes ont été évaluées pour déterminer la PEP optimale; cependant, des lacunes notables subsistent dans les données probantes à l'appui de leur utilisation. Il s'agit notamment de populations spécifiques (poumons normaux, patient·es sevré·es de la ventilation mécanique) et de l'utilisation d'autres critères d'évaluation (jours sans ventilateur et faisabilité) et cela représente d'importantes occasions pour des études futures.*

Enregistrement de l'étude *Open Science Framework (https://osf.io/atzqc); première publication, 19 juillet 2022.*

Keywords acute respiratory distress syndrome (ARDS) · hypoxemic respiratory failure · mechanical ventilation · optimal PEEP · positive end-expiratory pressure (PEEP)

Positive end-expiratory pressure (PEEP) is an important aspect of invasive mechanical ventilation that is set and titrated by clinicians. Changes in PEEP can influence gas exchange and respiratory mechanics, and can modify the risk of ventilatory-induced lung injury.[1,2] By extension, inappropriately high or low PEEP can worsen a patient's

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physiology and contribute to poor outcomes.[2] Determining the optimal or best PEEP is challenging and complex. Numerous methods to determine optimal PEEP have been tested; however, no single method has consistently been shown to be superior.[3] This has resulted in considerable variability in the clinical application of methods of determining optimal PEEP.[4–6]

There are several studies assessing methods of determining optimal PEEP, but certain methods, patient populations, and study settings lack high-quality evidence. A few large randomized controlled trials (RCTs) in patients with acute respiratory distress syndrome (ARDS) have compared methods such as high and low PEEP-F_IO_2 tables or titrating to a plateau pressure target but have been unable to show a change in mortality.[7–9] Many other methods lack RCTs or data on patient-centred or clinical outcomes.[10] Systematic reviews on determining optimal PEEP have generally been limited to methods that have been studied by RCTs, thereby excluding many other potentially viable methods.[11–15] Populations outside of ARDS are also underrepresented in high-quality trials of methods of determining optimal PEEP.

Our aim for this study was to describe the methods of determining optimal PEEP in adults undergoing invasive mechanical ventilation in both an intensive care unit (ICU) and operating room (OR) setting that have been reported in the literature. To accomplish the above aim, we used scoping review methodology to systematically identify types of evidence and to delineate gaps in the literature.[16] For each PEEP titration method, we sought to synthesize the patient populations, clinical and physiologic outcomes that have been studied, and the study designs that have been used. A better understanding of the gaps in the literature underpinning methods of determining optimal PEEP will guide clinical practice, identify areas of equipoise, and inform opportunities for further clinical trials.

Methods

Framework and registration

We registered this scoping review on 19 July 2022 on Open Science Framework (https://osf.io/atzqc). The protocol was peer-reviewed and published in advance.[17] We prepared the review in accordance with the most recent scoping review guidance.[18–20] The findings of our research are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review (PRISMA-ScR) statement and checklist[21] (see Electronic Supplementary Material [ESM] eAppendix).

Inclusion criteria

We developed our inclusion and exclusion criteria using the "Population, Concept, Context" framework.[20] Our population of interest was hospitalized adults receiving invasive mechanical ventilation. We excluded pediatric and neonatal populations, and those undergoing noninvasive or single lung ventilation. The concept of interest was a specific method of setting PEEP along with a measured outcome related to that method, either clinical or physiologic. We excluded studies that set PEEP at an arbitrary level. The context was broad, and we did not limit the searches by gender, geography, language, or duration of mechanical ventilation. We included only primary research studies and excluded case reports, systematic and other reviews, and editorials.

Search strategy

A medical librarian (H. L. R.) created search strategies for MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus based on the inclusion and exclusion criteria. The search strategy was peer-reviewed by a second medical librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist.[22] The search strategy for all databases can be found in ESM eTables 1–5. We completed the search on 22 April 2023 and included all results up to that date. The results were exported to Endnote 20 and screened using the systematic review software Rayyan (Qatar Computing Research Institute, 2016, Doha, Qatar).

Citation selection

Two reviewers (among S. E., N. K., K. P.) screened each citation to determine eligibility. Disagreements during title and abstract screening were resolved through discussion among the two reviewers and if consensus could not be reached, the third author would arbitrate. We then independently reviewed the full text of all eligible papers (K. P., S. E.) to finalize inclusion. We also reviewed reference lists of included papers and systematic reviews, and conference abstracts were included only if no corresponding manuscript was published. We translated non-English articles with Google Translate (Google LLC, Alphabet Inc., Mountain View, CA, USA) if an embedded PDF was available.[23] This approach has been validated for use in systematic reviews.[24]

Data abstraction

We abstracted relevant study data using a standardized form developed over several iterations with input from all members of the team and pilot testing of ten papers. Abstracted data related to 1) the citation (i.e., author, year and location of publication, journal, study design, funding); 2) population of interest and setting; 3) method of determining optimal PEEP; 4) other ventilator parameters (i.e., tidal volumes); and 5) outcomes (both primary and secondary). Abstracted data were collated in a Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet by one author (S. E.) and the charted data were verified and validated by a second author (K. P.).

Statistical analysis

Given the nature of scoping review methodology, we did not conduct a formal statistical analysis but presented descriptive statistics by summarizing characteristics of the included studies. Nominal data are presented as count (percent) and continuous data are presented as median [interquartile range (IQR)].

Results

Our search identified 10,874 unique citations, and we included 970 for full-text review. After full-text review, we included 271 articles studying 17,205 patients. Figure 1 shows the PRISMA flow diagram and reasons for exclusion at the full-text screening stage. The complete list of included studies (with study design, population, and method of determining optimal PEEP) can be found in ESM eTable 6.

Overall studies

Table 1 highlights characteristics of included studies. Of the 271 studies, 216 (80%) were set in the ICU including 13,157 patients, and 55 (20%) were set in the OR including 4,048 patients. The most common study designs were observational studies (163/271 studies, 60%, 5,479 patients), followed by RCTs (73/271 studies, 27%, 10,733 patients). The first ICU studies were published in the 1970s but the first OR study did not appear until 2006 (ESM eFig. 1). Half of the studies were among patients from Europe (139/271, 51%), but individuals from all continents were represented in the included studies (Table 1). Among the 216 studies performed in the ICU, most involved individuals with ARDS (n = 162, 75%). Among the 55 studies done in the OR, most patients had normal lungs (n = 46, 84%).

Methods of determining optimal positive end-expiratory pressure

We identified 22 different methods of PEEP selection (Table 2). We briefly describe each method along with strengths and limitations in Table 3.[7–10,25–97] All methods were studied in the ICU, whereas only seven of the 22 methods were studied in the OR (Table 2). More than one method was studied in 101 (37%) studies (eTable 6). In the ICU, the three most studied methods included the use of a PEEP-inspired fraction of oxygen (F_IO_2) table (n = 52 studies), imaging-based methods (n = 51 studies), and compliance-based methods (n = 46 studies). In the OR, the three most studied methods included compliance-based (n = 27 studies), imaging-based (n = 14 studies), and esophageal probe-based (n = 8 studies). Imaging-based methods of setting PEEP included electrical impedance tomography (EIT), ultrasound, and computed tomography. Of these, EIT was the most studied, comprising 83% of the imaging-based studies (n = 54) (eTable 7). Figure 2 shows the cumulative trend in publication over time among the five most studied methods of determining optimal PEEP in terms of overall studies and RCTs. The number of publications by five-year period among studies overall and RCTs can be seen in ESM eFig. 2.

Most common methods of determining optimal positive end-expiratory pressure

We present detailed descriptions of evidence supporting the eight most studied methods for determining optimal PEEP. These methods represent over 85% of the studies included in this scoping review (231/271 studies). Furthermore, these eight methods are studied in 72 of the 73 RCTs identified.

COMPLIANCE

Using respiratory system compliance to determine optimal PEEP was first reported in 1975[98] and was the most studied method (n = 73). Positive end-expiratory pressure was adjusted in an incremental or decremental fashion to maximize static or dynamic compliance. In many studies, this was preceded by recruitment maneuvers of varying intensity and frequency. This method can be used with any ventilator and no extra equipment or training is needed. Nevertheless, measuring static compliance requires patients to be passive on a ventilator, and serial measurements at different levels of PEEP can be time consuming. In addition, incremental and decremental PEEP trials can give different results. In the ICU setting, there were nine RCTs, two of which were multicentre trials. Both multicentre trials compared a compliance

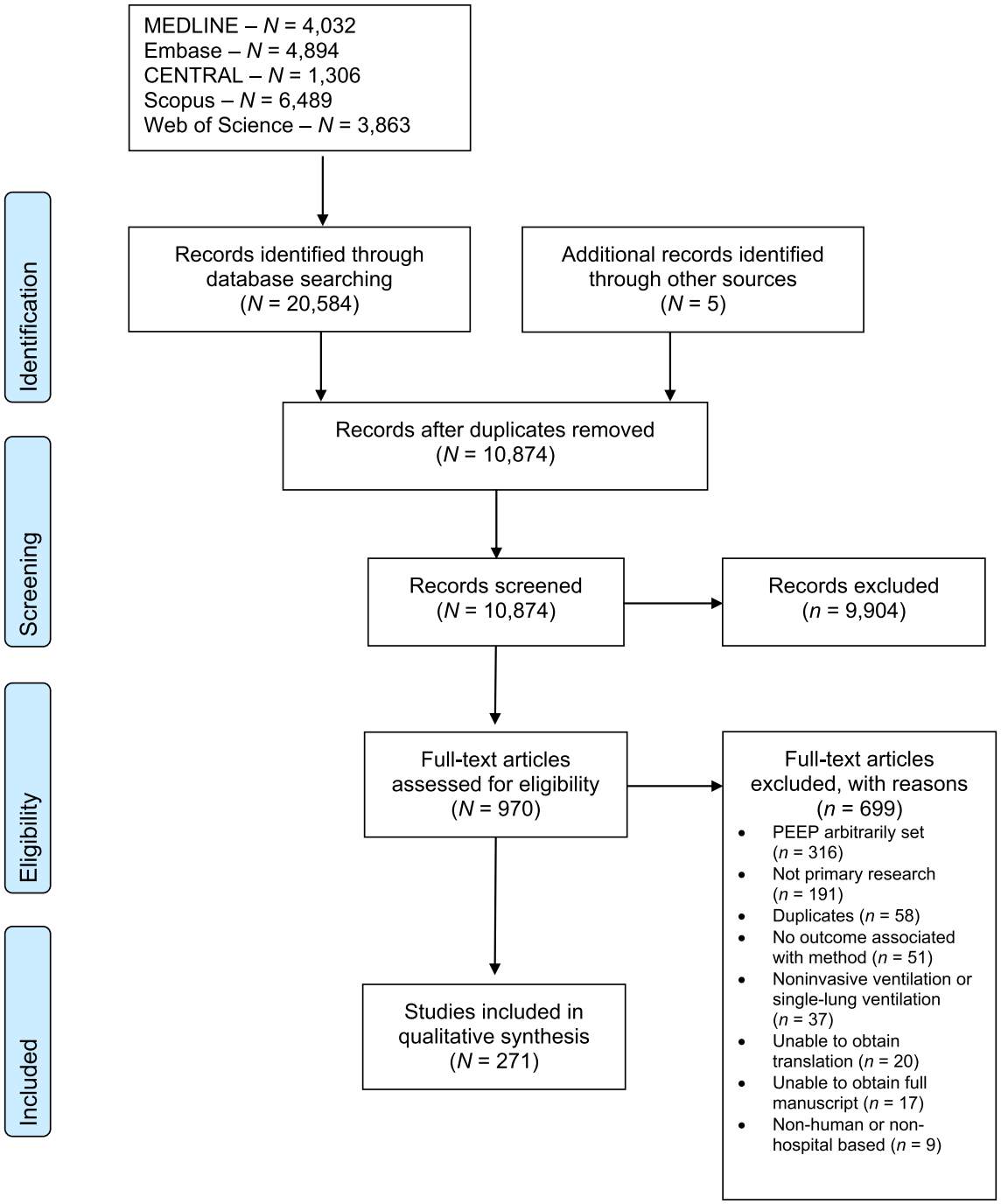

Fig. 1 PRISMA flow diagram

strategy with a low PEEP-F_IO_2 table. One found no difference in mortality or ventilator-free days (VFD).[25] The other found an increase in mortality with the compliance strategy,[26] although that arm was also accompanied by high pressure recruitment maneuvers. A large retrospective study compared PEEP determined by either compliance or pressure-volume curves in patients with ARDS being supported with extracorporeal membrane oxygenation (ECMO).[99] The compliance group had a shorter duration of mechanical ventilation, ICU length of stay (LOS), and hospital LOS. In the OR setting there were 20 RCTs, two of which were multicentre trials. One study randomized patients to a compliance strategy *vs* a fixed low PEEP.[35] The other study was a pilot RCT and compared compliance with PEEP set with an esophageal balloon or with a fixed

Table 1 Characteristics of included studies

Study characteristic	Number of studies*		
	Overall	ICU	OR
Number of studies, *N*	271	216	55
Study design, *n*/total *N* (%)			
Observational	163/271 (60%)	147/216 (68%)	16/55 (29%)
RCT	73/271 (27%)	39/216 (18%)	34/55 (62%)
Nonrandomized trial	14/271 (5%)	13/216 (6%)	1/55 (2%)
Randomized crossover	13/271 (5%)	12/216 (6%)	1/55 (2%)
Reanalysis	8/271 (3%)	5/216 (2%)	3/55 (6%)
Continent of origin,† *n*/total *N* (%)			
Europe	139/271 (51%)	114/216 (53%)	25/55 (46%)
Asia	67/271 (25%)	46/216 (21%)	21/55 (38%)
North America	38/271 (14%)	36/216 (17%)	2/55 (4%)
South America	19/271 (7%)	15/216 (7%)	4/55 (7%)
Africa	10/271 (4%)	8/216 (4%)	2/55 (4%)
Australia/New Zealand	9/271 (3%)	8/216 (4%)	1/55 (2%)
Time period, *n*/total *N* (%)			
1970s	4/271 (2%)	4/216 (2%)	0/55 (0%)
1980s	12/271 (4%)	12/216 (6%)	0/55 (0%)
1990s	10/271 (4%)	10/216 (5%)	0/55 (0%)
2000s	34/271 (13%)	32/216 (15%)	2/55 (4%)
2010s	100/271 (37%)	85/216 (39%)	15/55 (27%)
2020s	111/271 (41%)	73/216 (34%)	38/55 (69%)
Patient population,† *n*/total *N* (%)			
ARDS	162/271 (60%)	162/216 (75%)	0/55 (0%)
Normal	46/271 (17%)	0/216 (0%)	46/55 (84%)
Laparoscopic	30/271 (11%)	0/216 (0%)	30/55 (55%)
COVID-19	27/271 (10%)	27/216 (13%)	0/55 (0%)
Obese	25/271 (9%)	16/216 (7%)	9/55 (16%)
Mixed	22/271 (8%)	22/216 (10%)	0/55 (0%)
AHRF	12/271 (4%)	12/216 (6%)	0/55 (0%)
COPD	10/271 (4%)	10/216 (5%)	0/55 (0%)
Postoperative	10/271 (4%)	10/216 (5%)	0/55 (0%)
ECMO	10/271 (4%)	10/216 (5%)	0/55 (0%)
Proned	6/271 (2%)	4/216 (2%)	2/55 (4%)

Included studies are stratified by overall and study setting

*Percentages are for total studies within given column

†Sum of columns is greater than total as some articles fit more than one category

AHRF = acute hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; OR = operating room; RCT = randomized controlled trial

low PEEP.[48] Both found no difference in postoperative complications.

PEEP-F_IO_2 TABLES

PEEP-F_IO_2 tables were first used along with low tidal volume ventilation in the landmark ARDSNet trial in 2000.[100] The tables were developed based on the clinical practice of the study sites participating in the trial.[101] The tables were not prospectively tested as a method until 2004 when the same authors published an RCT comparing low and high PEEP-F_IO_2 tables.[7] Since then, most large multicentre RCTs in patients with ARDS have used a PEEP-F_IO_2 table as the comparator. This method involves a table that specifies a value or range of values for PEEP

Table 2 Number of studies published assessing different methods of determining optimal positive end-expiratory pressure

PEEP method*	Overall, *n*/total *N* (%)	Setting, *n*/total *N* (%)*		RCTs, *n*/total *N* (%)†
		ICU	OR	
All studies	271	216	55	73
Compliance	73/271 (27%)	46/216 (21%)	27/55 (49%)	29/73 (40%)
Imaging-based	65/271 (24%)	51/216 (24%)	14/55 (26%)	11/73 (15%)
PEEP-F_IO_2 table	53/271 (20%)	52/216 (25%)	0/55 (0%)	21/73 (29%)
Esophageal probe	49/271 (18%)	41/216 (19%)	8/55 (15%)	11/73 (15%)
Oxygenation	40/271 (15%)	35/216 (16%)	5/55 (9%)	12/73 (16%)
Pressure-volume curves	23/271 (9%)	23/216 (11%)	0/55 (0%)	7/73 (10%)
Plateau pressure	12/271 (4%)	12/216 (6%)	0/55 (0%)	2/73 (3%)
Driving pressure	11/271 (4%)	5/216 (2%)	6/55 (11%)	7/73 (10%)
Computer-based	11/271 (4%)	11/216 (5%)	0/55 (0%)	1/73 (1%)
Shunt	10/271 (4%)	10/216 (5%)	0/55 (0%)	2/73 (3%)
Auto-PEEP	8/271 (3%)	8/216 (4%)	0/55 (0%)	0/73 (0%)
EELV/FRC	7/271 (3%)	5/216 (2%)	2/55 (4%)	1/73 (1%)
Dead space	6/271 (2%)	4/216 (2%)	2/55 (4%)	0/73 (0%)
Intra-abdominal pressure	4/271 (2%)	3/216 (1%)	1/55 (2%)	0/73 (0%)
Stress index	3/271 (1%)	3/216 (1%)	0/55 (0%)	0/73 (0%)
Oxygen delivery	2/271 (1%)	2/216 (0.9%)	0/55 (0%)	0/73 (0%)
Airway opening pressure	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)
Airway occlusion pressure	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)
NAVA	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)
R/I ratio	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)
Time constant	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)
Weight	1/271 (0.4%)	1/216 (0.5%)	0/55 (0%)	0/73 (0%)

Studies that published assessing different methods of determining optimal positive end-expiratory pressure are stratified by overall, study setting, and number of RCTs for each method

*Sum of columns is greater than total as some articles fit more than one category

†Percentages are for total studies within given column

EELV = end-expiratory lung volume; FRC = functional residual capacity; ICU = intensive care unit; NAVA = neurally adjusted ventilatory assist; OR = operating room; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; R/I = recruitment to inflation

for a given F_IO_2 that the patient requires to maintain oxygen saturation within a certain range. The higher the required F_IO_2, the higher the PEEP specified. This method has the advantage that it can be used without any extra equipment and in patients who are spontaneously breathing. It is quick and simple to implement with little cost. This method does not consider a patient's respiratory mechanics. It has been assessed in 53 studies. In the ICU setting, 21 RCTs were published, seven of which were multicentre RCTs. All seven compared a PEEP-F_IO_2 table to another method of determining optimal PEEP (two of the studies compared high *vs* low tables[7,9]) in patients with ARDS. All had a primary outcome of either mortality, VFD, or a composite of the two, and only one had a statistically significant difference showing reduced mortality with a low PEEP-F_IO_2 table compared with a method using compliance and lung recruitment maneuvers.[25] A retrospective cohort study of patients with ARDS due to COVID-19 compared those who had PEEP set at levels close to the low PEEP-F_IO_2 table and those who had PEEP set at levels close to the high PEEP-F_IO_2 table.[102] After propensity score matching, the higher PEEP group was associated with more VFD but also had a greater likelihood of acute kidney injury and renal replacement therapy. This method has not been studied in an OR setting to date.

Electric impedance tomography

Studies using imaging to determine optimal PEEP have gained considerable interest in the last decade, most commonly with EIT (54 studies). The method was first described in an OR setting in 2006[103] and subsequently in an ICU setting in 2015.[104] In less than ten years, 42 papers

Table 3 Methods of positive end-expiratory pressure selection

Method of PEEP titration	Description	Strengths	Limitations	RCTs, *n*
Compliance	Selection based on highest static or dynamic compliance.[26] Assessed by either incremental or decremental stepwise PEEP trial with or without a recruitment maneuver.	Able to be calculated with any ventilator at the bedside. No additional equipment.	Patient must be passive on ventilator. Takes time to do incremental or decremental trials.	29[25–41,43–48,82,87,90,91,93,94]
PEEP/F_IO_2 table	Selected via table that assigns a PEEP (or range of PEEPs) for a given F_IO_2. There are low PEEP and high PEEP/F_IO_2 tables, as seen in ALVEOLI trial.[7]	Simple, requires no equipment, can be reassessed regularly, minimal time investment	Does not take into consideration patient's mechanics	21[7,9,25–32,49–59]
Oxygenation	Selection by change in oxygenation (SpO_2 or PaO_2) during either a decremental[56] or incremental[64] stepwise trial, or maximal oxygenation within a defined range[65]	Able to be calculated with any ventilator at the bedside	Requires arterial blood gas for PaO_2. Does not assess mechanics.	12[45,47,54–56,62,64–67,84,88]
Esophageal probe	Pressure transduced from esophageal balloon as surrogate for pleural pressure[50] PEEP is titrated to end-expiratory transpulmonary pressure > 0 cm H_2O	Partitioning of lung and chest wall mechanics, measuring true pressures affecting the lungs	Special equipment, ventilators, and education	11[30,33,48–50,52,60–63,85]
Imaging—EIT	Maps out areas of collapse, normal aeration, and overdistension within the lung.[10] PEEP set to minimize both collapse and overdistension[51] or to lowest RVDI.[68]	Noninvasive bedside method of determining degree of collapse and overdistension	Requires special equipment, monitoring supplies, and education	8[30,43,51,68–71,89]
Pressure-volume curves	Curve generated with single breath[69] or plotting breaths of varying volumes.[72] PEEP set above the lower inflection point[72] or at the point of maximal hysteresis.[69]	Provides information about respiratory system mechanics	Patient must be passive on ventilator. Plotting curve takes time. Few ventilators can do single breath curve.	7[69,72–76,92]
Driving pressure	Difference between plateau pressure and PEEP. PEEP can be set at the level that corresponds to the lowest driving pressure during an incremental trial.[42]	Able to be calculated with any ventilator at the bedside. No additional equipment.	Patient must be passive on ventilator. Takes time to do incremental trials.	7[42,57,79,83,86,95,97]
Imaging—ultrasound	PEEP adjusted to optimize aeration as assessed by presence or absence of artifact on lung ultrasound. Can be incremental[121] or decremental.[109]	Able to be measured independent of ventilator mode	Requires training in ultrasound and interrater reliability can be an issue	3[58,59,122]
Plateau pressure	For a given tidal volume, PEEP can be increased until a plateau pressure of 28–30 cm H_2O is achieved[8]	Able to be calculated with any ventilator at the bedside. Can be reassessed quickly.	Patient must be passive on ventilator	2[8,53]
Shunt	Shunt fraction (Qs/Qt) can be calculated using blood from an arterial catheter and a PA catheter. PEEP adjusted for reduction in shunt fraction[66] or an absolute value.[64]	Best measure of oxygenation of the lungs overall. Patient does not need to be paralyzed.	Requires PA catheter. Does not take into consideration patient's mechanics.	2[64,66]
EELV	EELV (absolute or change) is measured by several techniques including plethysmography[123] and nitrogen multiple breath washout technique[67]	Direct measure of recruitment with different levels of PEEP	Requires specialized equipment	1[67]

Table 3 continued

Method of PEEP titration	Description	Strengths	Limitations	RCTs, *n*
Computer-based	Certain ventilators have software such as Intellivent-ASV[80] that will automatically adjust variables including PEEP based on certain inputs	Automated methods require little workforce and can adjust as conditions change	Modes are proprietary to different ventilators and may not be available for all patients	1[96]
Airway occlusion pressure ($P_{0.1}$)	$P_{0.1}$ is pressure measured in first 0.1 sec of inhalation against occluded airway and is surrogate of respiratory drive can be set to keep $P_{0.1}$ within a range	Useful in patients weaning. Noninvasive. Most modern ventilators can perform.	Not useful in deeply sedated or paralyzed patients	0
AOP	Low-flow inflation maneuver is done with PEEP 0 cm H_2O. Inflection in slope of pressure-time curve is noted as AOP. PEEP is set at or above that level.	Can be measured with any ventilator. Assesses lung mechanics.	Patient must be passive on ventilator. Does not consider hysteresis.	0
Auto-PEEP	Calculated by subtracting total PEEP (measured with end-expiratory hold) from applied PEEP. PEEP is set to a percentage of auto-PEEP between 50% and 100%.	Can be measured with any ventilator. Considers mechanics and can aid in work of breathing.	Limited value in patients without airflow obstruction. Must be passive on ventilator to perform.	0
Dead space	Dead space can be calculated using volumetric capnography[124–126] and Bohr's equation. PEEP can be set to reduce or minimize dead space fraction	Continuously monitored. Patient can breathe spontaneously. Measures ventilatory efficiency.	Volumetric capnography requires special equipment. Does not consider mechanics.	0
Imaging—CT	CT is done at a baseline PEEP, after recruitment, and images are taken as PEEP is gradually decreased. PEEP is set above the level at which lung closure occurs.	Accurate way to measure recruitment and visualize overdistension	Patient must be passive on ventilator. Resource intensive and requires transporting patients.	0
IAP	IAP is measured (via bladder pressure) and PEEP is set at a percentage (from 50%[127] to 125%[128]) of IAP	Simple to perform. Can easily trend. Accounts for mechanics.	Limited value in patients with normal IAP. Patient must be passive to measure accurate IAP.	0
NAVA	NAVA is a mode of ventilation that measures the EAdi with an esophageal catheter. PEEP can be set at the level that has optimal EAdi.[81]	Accurate way to ensure good patient-ventilator synchrony and assist	Requires special equipment and invasive monitors	0
Oxygen delivery	DO_2 is calculated with PaO_2 and cardiac output using transesophageal doppler[129] or echocardiography.[130] PEEP is adjusted to maximize DO_2.	Considers oxygenation as well as the hemodynamic consequences of PEEP	Requires special equipment and training. Does not consider mechanics.	0
R/I ratio	Recruitment between two levels of PEEP is inferred based on changes in mechanics and change in EELV. PEEP set based on recruiter *vs* nonrecruiter.	Can be measured with any ventilator	Patient must be passive on ventilator	0
Stress index	Shape of pressure-time waveform. Upslope at end-inspiration indicates overdistension, and downslope indicates recruitment. PEEP is set to target linear or decreasing index.	Can be measured with any ventilator. Can be monitored continuously. Assesses mechanics.	Patient must be passive on ventilator	0

Table 3 continued

Method of PEEP titration	Description	Strengths	Limitations	RCTs, *n*
Time constant	Using a constant driving pressure, PEEP is adjusted and set at the level corresponding to the highest time constant	Can be measured with any ventilator	Patient must be passive on ventilator	0
Weight	PEEP set based on BMI. Stratified BMI by < 30 kg·m^{-2}, 30–50 kg·m^{-2}, and > 50 kg·m^{-2}.	Simple method. May compensate for higher pleural pressures in patients with obesity.	BMI does not consider distribution of body mass. Does not measure mechanics or oxygenation.	0

AOP = airway opening pressure; ASV = adaptive supportive ventilation; BMI = body mass index; CT = computed tomography; DO_2 = oxygen delivery; EAdi = electrical activity of the diaphragm; EELV = end-expiratory lung volume; EIT = electrical impedance tomography; F_IO_2 = inspired fraction of oxygen; IAP = intra-abdominal pressure; NAVA = neurally adjusted ventilatory assist; PaO_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure; PA = pulmonary artery; Qs = pulmonary physiologic shunt (mL·min^{-1}); Qt = cardiac output (mL·min^{-1}); R/I = recruitment to inflation; RCT = randomized controlled trial; Ref = reference; RVDI = regional ventilation delay index; SpO_2 = peripheral oxygen saturation

on setting PEEP with EIT in the ICU have been published. Electrical impedance tomography measures the impedance between leads placed across a patient's chest to map areas of the lungs with normal aeration, overdistension, and collapse. Studies have set PEEP by determining the optimal level that minimizes both overdistension and collapse as determined by EIT. This method has shown promise as a noninvasive bedside test that can help clinicians assess regional differences within the lungs. Nevertheless, it has several limitations. Most notably, it requires purchasing equipment and conducting training, and in nearly all studies required patients to be passive on the ventilator. In the ICU setting, there were two published single-centre RCTs, neither of which found a difference in outcome between the EIT arm and either a low PEEP-F_IO_2 table[51] (mortality) or use of a pressure-volume curve[69] (physiologic measures). A prospective observational study compared patients with ARDS whose PEEP was determined using EIT with a historical cohort that used a pressure-volume to determine optimal PEEP.[105] The EIT group had improved compliance but no difference in mortality. In the OR setting, there were five single-centre RCTs. Most used physiologic endpoints except for one, which found a reduction in postoperative hypoxemia compared with a fixed low-PEEP strategy.[89]

Esophageal balloons

Esophageal balloons were first used to determine optimal PEEP in a single-centre RCT in 2008[50] and, to date, 50 studies have assessed this method. These devices measure esophageal pressure, which can estimate the pleural pressure and calculate transpulmonary pressure. The PEEP is set to ensure transpulmonary PEEP is zero or slightly positive. This method could be more accurate in reflecting lung physiology *vs* other methods that assess mechanics using airway pressures, especially if the chest wall pressures are abnormal. One advantage of this method is that the balloon can detect pressures generated by the diaphragm; therefore, this method can accurately estimate distending pressures in patients who are spontaneously breathing. Nevertheless, it requires extra equipment and training to use, and insertion can be time consuming. In the ICU setting, seven RCTs were published, one of which was a multicentre RCT in patients with ARDS comparing esophageal balloon with a high PEEP-F_IO_2 table.[49] It found no difference in the composite primary outcome of mortality and VFD. A *post hoc* analysis of that trial found that, among patients with lower Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, the esophageal balloon group had lower mortality. The inverse relationship was true in those with higher APACHE-II scores, although the relationship was not statistically significant ($P = 0.08$).[106] This method was tested in the only RCT of patients being weaned from mechanical ventilation,[33] likely because of its utility in spontaneously breathing patients. There was no difference in duration of mechanical ventilation between this method and PEEP determined by best compliance. A retrospective study compared PEEP determined with an esophageal balloon with a fixed PEEP of 10 cm H_2O in patients with ARDS being supported by ECMO.[107] The esophageal balloon group had less hemodynamically significant right ventricular dysfunction and improved survival to ECMO

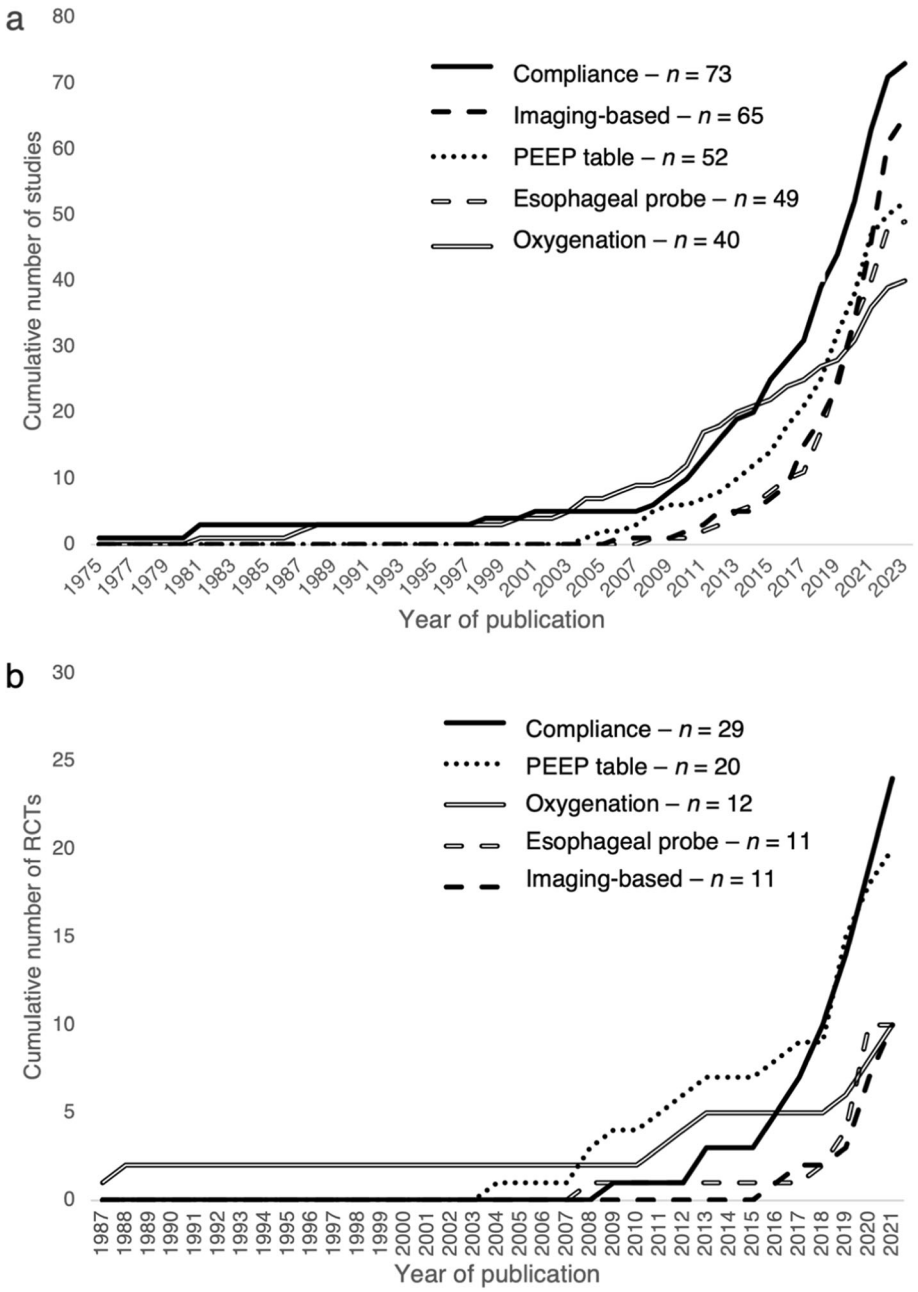

Fig. 2 Cumulative number of studies assessing methods of determining optimal positive end-expiratory pressure over time, stratified by method. (a) Overall number of studies published; (b) randomized controlled trials published.

PEEP = positive end-expiratory pressure; RCT = randomized controlled trials

decannulation. In the OR setting, four RCTs were published, one of which was a multicentre RCT. All four RCTs had primary physiologic endpoints. Three found a significant difference favouring the esophageal balloon, with improvements in driving pressure,[48,60,62] compliance,[48,62] and oxygenation[62] compared with either an oxygenation[62] or low fixed PEEP[48,60] strategy. One of the studies also had a third arm using a compliance strategy and found similar outcomes in terms of respiratory mechanics.[48]

Oxygenation

Oxygenation was first used as a target for setting PEEP in 1981, when it was studied in postoperative surgical ICU patients.[108] There were 40 studies assessing this method. Several variations exist that use oxygenation or change in

oxygenation to determine optimal PEEP. Incremental or decremental stepwise trials are done with or without lung recruitment maneuvers beforehand, with PEEP set at the level with the highest level of oxygenation or change in oxygenation. This can be measured via pulse oximetry or blood gas analysis. This method does not require any special equipment but may require an arterial line and frequent blood gas sampling if PaO_2 is used. The method is less resource intensive with pulse oximetry but could be time consuming if incremental or decremental stepwise trials are done. In the ICU setting, there were 11 RCTs, three of which were multicentre RCTs. These were done mainly in patients with ARDS or acute hypoxemic respiratory failure (AHRF). Two multicentre trials—one done in patients with ARDS with a low PEEP-F_IO_2 table comparator[56] and the other in patients without ARDS with a PEEP 0–5 cm H_2O comparator[65]—found no difference in their primary outcome of VFD. The third multicentre RCT compared oxygenation with the use of a pressure-volume loop to determine optimal PEEP, but its primary endpoint was biochemical markers.[92] The pressure-volume loop group had a reduction in cytokines and inflammatory markers. A prospective nonrandomized trial studied patients with ARDS and atelectasis, comparing PEEP set with oxygenation and PEEP set with lung ultrasound.[109] The lung ultrasound group had improved oxygenation, but no change in compliance, and a greater drop in blood pressure during the procedure. In the OR setting, there were three single-centre RCTs, all with primary physiologic endpoints. One compared oxygenation with the use of an esophageal balloon and found better oxygenation, compliance, and driving pressure in the esophageal balloon group.[62] The other two compared either oxygenation alone[84] or a combination of oxygenation and compliance[47] with a low fixed PEEP and found these strategies superior to fixed PEEP in terms of oxygenation.

Pressure-volume loops

The pressure-volume loop was first used for determining optimal PEEP in 1,987 in patients with AHRF,[110] and 23 studies have since assessed this method. In that study and others in the period, pressure-volume loops were measured using a large 2-L syringe attached to a pressure transducer. In more recent studies, the loops are generated with ventilators either by manually plotting the curve with increasing tidal volumes, or with a single breath technique. The latter is only possible with certain ventilators. The level of PEEP is typically set at or just above the lower inflection point of the inspiratory limb of the pressure-volume loop or is sometimes set at the point of maximum hysteresis between the inspiratory and expiratory limbs. This technique assesses many aspects of a patient's respiratory mechanics but can be time consuming, requires extra training and equipment, and the patient must be passive on the ventilator. In the ICU setting, seven RCTs were completed in patients with ARDS and one RCT in postcardiac surgery patients. Two of these were multicentre RCTs, both studying patients with ARDS. One mentioned above compared oxygenation with pressure-volume loop methods, but had biochemical markers as the primary endpoint.[92] The pressure-volume loop group had a reduction in cytokines and inflammatory markers. The other compared PEEP set with a pressure-volume loop to PEEP set at the clinician's preference. This study found a benefit in ICU mortality in the pressure-volume loop arm.[74] Nevertheless, tidal volumes differed between arms, making it difficult to assess the effect of the PEEP strategy alone. This method has not been studied in an OR setting.

Driving pressure

Driving pressure was first used to determine optimal PEEP in 2016 in patients with obesity without ARDS.[111] There were 11 studies assessing this method. PEEP can be adjusted to the highest level that keeps driving pressure under a given threshold (in one study $\leq$ 14 cm H_2O[57]) or can be adjusted within a given range to a value that yields the lowest driving pressure. Driving pressure is inversely correlated to compliance. For a fixed tidal volume, an increase in compliance will result in a proportional decrease in driving pressure. This method can be performed with any ventilator without extra training or equipment. Nevertheless, testing driving pressure at several PEEP levels can be time consuming, and patients must be passive on the ventilator to measure an accurate driving pressure. In the ICU setting, there was only one RCT in patients with ARDS.[57] It was a single-centre study comparing use of driving pressure with a low PEEP-F_IO_2 table to determine optimal PEEP. There was a statistically significant difference in 28-day mortality favouring the driving pressure group. In the OR setting, there were five single-centre RCTs, all comparing the driving pressure method with a low fixed PEEP. Of the two that had a clinical endpoint of postoperative complications, both favoured driving pressure.[42,86]

Plateau pressure

Plateau pressure was first used to determine optimal PEEP in 2003 in patients with ARDS.[112] Positive end-expiratory pressure is increased until the patient's plateau pressure hits a certain level, typically between 28 and 30 cm H_2O. This method can be done with any ventilator without extra

training and is fast. Nevertheless, to obtain an accurate plateau pressure, patients must be passive on the ventilator. In the ICU setting, there were two RCTs, both of which were large multicentre trials of patients with ARDS. One study compared this method to a fixed PEEP of 5–9 cm H_2O[8] and the other used a low PEEP-F_IO_2 table.[53] Mortality was the primary endpoint in both studies, and neither found a difference between the two arms, although the first study showed a reduction in their secondary outcome of VFD in the plateau pressure group.[8] This method has not been studied in an OR setting.

Description of randomized controlled trials

Eleven of the 22 methods were studied with at least one RCT and we identified 73 RCTs overall with 10,708 patients. Table 4 shows the characteristics of the included RCTs. Four of the RCTs were reported in abstract format and have not yet been published. The remaining 69 RCTs were published in 46 different medical journals (ESM eTable 8). Of the 73 RCTs, 31 directly compared two different methods of determining optimal PEEP (ESM eTable 6). The sample sizes of the RCTs ranged from 12 to 1,012 patients with a median [IQR] of 60 [40–115]. The distribution in the number of patients enrolled in RCTs among ICU and OR studies is summarized in ESM eFig. 3. The RCTs included participants from 35 different countries. Six RCTs contained participants from multiple countries. The four countries with the largest number of trials conducted were China (n = 18), USA (n = 9), Brazil (n = 7), and Spain (n = 7) (ESM eTable 9). Over half of the studies were publicly funded (38/73, 52%). Most RCTs were single-centred, with 19% being multicentred (n = 14). Among the 39 RCTs done in an ICU setting, 82% involved patients with ARDS (n = 32). Among the 34 RCTs done in the OR, 91% involved participants with normal lungs (n = 31). In 58% of the RCTs (n = 42), a difference in the primary outcome was reported, which was considered statistically significant (ESM eTable 10). Tidal volumes were standardized within treatment arms in 74% of the RCTs (n = 54). Of these, all but one used low tidal volume ventilation whereas the other arms were ventilated initially at 12 cc/kg.[66]

Outcomes among randomized controlled trials

Most of the RCTs had a physiologic measure as the primary outcome (n = 39, 53%). This was more common among RCTs in the OR (23/34, 68%) compared with RCTs in the ICU (16/39, 41%). The most common physiologic measures used as a primary outcome were oxygenation and compliance. Among the RCTs with a physiologic measure as the primary outcome, the difference in the primary endpoint was statistically significant in 69% of studies (n = 27) (ESM eTable 10).

Only RCTs conducted in the ICU had mortality as a primary outcome (n = 14, 36%). Among RCTs, mortality was recorded as an outcome (whether primary or secondary) in 77% (30/39) of studies done in the ICU compared with 18% (6/34) of studies done in the OR. The most common measures of mortality were 28-day mortality (n = 21, 29%), hospital mortality (n = 19, 26%), and ICU mortality (n = 15, 21%) (ESM eTable 11). Among the RCTs that used mortality as the primary outcome, the difference in the primary endpoint was statistically significant in 36% of studies (n = 5) (ESM eTable 10).[25,57,66,72,74]

For other clinically relevant outcomes, 77% (30/39) of RCTs conducted in the ICU measured a ventilation outcome compared with 53% (18/34) of RCTs done in the OR. The two most common measures were duration of mechanical ventilation (n = 34, 47%) and VFD at 28 days, which is a composite of mortality and ventilation (n = 16, 22%) (ESM eTable 11). Length-of-stay outcomes were measured in 62% (24/39) of ICU studies and 38% (13/34) of OR studies. The most common measures were ICU LOS (n = 31, 43%) and hospital LOS (n = 29, 40%) (ESM eTable 11). Most studies (n = 52, 71%) reported some safety outcome. The most common safety outcome was barotrauma in ICU studies (26/39, 67%) and hemodynamic instability in OR studies (24/34, 71%) (ESM eTable 11). Four studies assessed outcomes related to costs and/or feasibility of certain strategies. One study qualitatively discussed the cost-effectiveness of a certain strategy,[35] while three others measured the time involved with certain strategies.[29,58,96]

Discussion

In this scoping review, we synthesized 271 articles published over 48 years that reported assessments of methods of determining optimal PEEP in hospitalized individuals receiving mechanical ventilation. Among these studies, there were 22 different methods of selecting PEEP. Only 11 of these methods were studied with an RCT. Patients with ARDS in an ICU were most studied with 162 studies and 32 RCTs. There is a growing body of literature looking at patients ventilated in the OR, especially in the last decade, with 55 studies and 34 RCTs. The majority of RCTs set in the ICU measured a clinically relevant primary outcome such as mortality or duration of mechanical ventilation. Most RCTs done in the OR used a physiologic endpoint such as oxygenation or compliance as the primary outcome.

It is unsatisfying that, despite the large number of published studies, the very large number of participants studied, and a diversity of methods for determining optimal

Table 4 Characteristics of included randomized controlled trials

Study characteristic	Overall, *n*/total *N* (%)	Setting, *n*/total *N* (%)*	
		ICU	OR
Overall	73	39	34
Study design, *n*/total *N* (%)			
Multicentred	14/73 (19%)	12/39 (31%)	2/34 (6%)
Multinational	6/73 (8%)	6/39 (15%)	0/34 (0%)
Number of individuals randomized, median [IQR]	60 [40–115]	61 [39–123]	56 [41–91]
Funding, *n*/total *N* (%)			
Publicly funded	38/73 (52%)	19/39 (49%)	19/34 (56%)
Not reported	26/73 (36%)	17/39 (44%)	9/34 (27%)
No funding	8/73 (11%)	2/39 (5%)	6/34 (18%)
Industry funded	1/73 (1%)	1/39 (3%)	0/34 (0%)
Patient population, *n*/total *N* (%)			
ARDS	32/73 (44%)	32/39 (82%)	0/34 (0%)
Normal	31/73 (43%)	0/39 (0%)	31/34 (91%)
Laparoscopic	22/73 (30%)	0/39 (0%)	22/34 (65%)
Obese	4/73 (6%)	1/39 (3%)	3/34 (9%)
Postoperative	3/73 (4%)	3/39 (8%)	0/34 (0%)
AHRF	2/73 (3%)	2/39 (5%)	0/34 (0%)
ECMO	2/73 (3%)	2/39 (5%)	0/34 (0%)
Mixed	2/73 (3%)	2/39 (5%)	0/34 (0%)
Outcomes, *n*/total *N* (%)			
Type of primary outcome			
Physiologic	39/73 (53%)	16/39 (41%)	23/34 (68%)
Oxygenation	27/73 (37%)	12/39 (31%)	15/34 (44%)
Compliance	12/73 (16%)	4/39 (10%)	8/34 (24%)
Mortality	14/73 (19%)	14/39 (36%)	0/34 (0%)
Other	8/73 (11%)	4/39 (10%)	4/34 (12%)
Postoperative complication	6/73 (8%)	0/39 (0%)	6/34 (18%)
Ventilator-free days	4/73 (6%)	4/39 (10%)	0/34 (0%)
Not reported	2/73 (3%)	2/39 (5%)	0/34 (0%)
Duration of ventilation	1/73 (1%)	1/39 (3%)	0/34 (0%)
Reported by any study			
Safety outcomes	52/73 (71%)	28/39 (72%)	24/34 (71%)
Length of stay	37/73 (51%)	24/39 (62%)	13/34 (38%)
Mortality	36/73 (49%)	30/39 (77%)	6/34 (18%)
Duration of ventilation	34/73 (47%)	16/39 (41%)	18/34 (53%)
Postoperative complication	23/73 (32%)	0/39 (0%)	23/34 (68%)
Ventilator-free days	19/73 (26%)	19/39 (49%)	0/34 (0%)
Costs/feasibility	4/73 (6%)	3/39 (8%)	1/34 (3%)
Tidal volumes between arms, *n*/total *N* (%)			
Same tidal volumes	54/73 (74%)	27/39 (69%)	27/34 (79%)
Different tidal volumes	13/73 (18%)	8/39 (21%)	5/34 (15%)
Not reported	6/73 (8%)	4/39 (10%)	2/34 (6%)

Included randomized controlled trials are stratified by overall and trial setting

*Percentages are for total studies within given column

AHRF = hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile ratio; OR = operating room

PEEP, the ideal strategy remains elusive. This is reflected in recommendations from recent guidelines on ARDS, which abstain from recommending which method should be used to set PEEP.[113] This review illustrates several explanations as to why there is lack of consensus on which method is the best. One major driver is the variation in quantity and quality of research for each method, which makes it challenging to determine if any given one may be superior. For example, 11 methods have not been studied with an RCT. These methods were investigated with observational studies, many without comparator groups. It is difficult to evaluate these methods due to the higher risk of bias and confounding with these study designs. Furthermore, 83% (166/199) of the nonrandomized studies had fewer than 50 participants, which may limit power to detect differences in clinically meaningful outcomes. Nevertheless, these studies can be helpful in generating hypotheses that can be tested with randomized trials. Among those studied with an RCT, there is variability in population, setting, comparators, and outcomes, which limits the ability to pool and meta-analyze these studies.

Many systematic reviews have attempted to synthesize the data within specific populations, including patients with ARDS,[11–15] ICU patients without ARDS,[114,115] and patients undergoing surgery.[116,117] Nevertheless, they often include studies that arbitrarily set PEEP at a certain level and have not directly compared specific strategies or methods of determining optimal PEEP. Instead, many systematic reviews elect to group PEEP levels into high or low groups. Li *et al*. is the only meta-analysis that compared "individualized PEEP" with PEEP set at arbitrary low, moderate, or high levels in the intraoperative setting, but did not distinguish between different methods used to individualize.[116] The establishment of a superior method was not the objective of this scoping review; however, the breadth of methods in this scoping review and its associated variability in population, setting, and outcomes studied shows why equipoise remains.

This scoping review has helped identify important patient populations that could benefit from further study. We found an abundance of studies of patients with ARDS in the ICU (75% of overall studies and 82% of RCTs), but other populations were lacking in robust RCTs. For example, very few studies examined ICU patients without ARDS, those who were weaning from mechanical ventilation, or patients with chronic obstructive pulmonary disease (COPD). Only one RCT in the past 20 years has assessed a method of determining optimal PEEP in patients without ARDS in the ICU[65] and one RCT of patients with obesity weaning from mechanical ventilation.[33] Given that patients without ARDS or those who are weaning may be on spontaneous modes of mechanical ventilation, many of the methods described are difficult or impossible to perform in these clinical settings. We identified ten studies in patients with COPD, most of which used a patient's auto-PEEP to determine the set PEEP.[118–120] Neither that population nor method has been studied with a randomized trial. Future studies in these populations could inform guidelines and potentially simplify care if different methods of determining optimal PEEP have no influence on the outcomes of these patients.

This scoping review illustrates that many of the previous trials and systematic reviews have used mortality as the primary outcome.[11,12,14] Of the RCTs that used similar tidal volumes between arms and measured mortality as the primary outcome, only two out of ten found a significant difference.[25,57] In contrast to mortality, alternative outcomes like the duration of mechanical ventilation or a composite outcome such as VFD may be more illustrative of its benefits given the effects PEEP has on compliance, oxygenation, and recruitment. Ventilator-free days were measured in many RCTs, and this outcome has only been synthesized in terms of high *vs* low PEEP[11,15] but not synthesized by method of determining optimal PEEP.

Many other outcomes are also important but are rarely measured. Cost-effectiveness and ease of implementation and use between methods is relevant, especially if there is equipoise between two methods on mortality or other clinical outcomes. For example, a PEEP-F_IO_2 table requires no extra equipment and takes little to no time to set PEEP. Contrast this with EIT, which requires special equipment and takes longer or a compliance-based method, which requires patients to be deeply sedated or paralyzed to prevent spontaneous efforts. If two methods have equivalent efficacy on mortality and other clinical outcomes but one is quicker and cheaper to implement, it could be argued that it is the superior method. We identified only three RCTs that measured the time associated with a specific PEEP method[29,58,96] and none did a formal cost-analysis. In centres with limited staff and limited resources, these differences could be important for implementation and should be studied further.

Our review should be interpreted in the context of its limitations. We were unable to access several papers because of difficulties either obtaining or translating them (ESM eTable 12). Nevertheless, we were thorough and comprehensive in our attempts. For some articles that were inaccessible via our institutional access, we e-mailed authors (if an e-mail address was available) to request a copy of the manuscript. For non-English articles, we translated any PDFs that were compatible with Google Translate. Some articles could not be translated and thus were not included in the qualitative analysis. Another limitation is that, because we chose to perform a scoping

review, we did not perform risk of bias assessments on the included studies or synthesize any of the outcomes as this is not the goal or purpose of a scoping review. In addition, although we included a large number of studies, many of the included studies were observational and not RCTs. Observational studies may show association but not causality and may also be at risk of bias because they cannot adjust for unmeasured confounders.

Our review also has several strengths. We developed a rigorous search strategy with a librarian and searched five databases. We also developed a framework and used predefined inclusion and exclusion criteria and assessed consistency in screening, inclusion, and data abstraction. We described not only RCTs but also nonrandomized studies pertaining to methods of determining optimal PEEP, thereby including many more methods. With the RCTs, we abstracted detailed information about the important primary and secondary outcomes, including less reported outcomes such as safety, feasibility, and cost.

Using scoping review methodology, we identified a spectrum of methods of determining optimal PEEP among mechanically ventilated patients. We included studies using 22 different methods from a variety of settings, with different populations, different study designs, and assessing different outcomes. We identified important gaps in the literature, including more robust nonmortality outcomes such as ventilator-free survival among patients with ARDS, as well as populations that warrant further study including patients with normal lungs as well as those on spontaneous modes of ventilation who are weaning from mechanical ventilation. Future studies should address these gaps and should incorporate measures of feasibility when comparing different methods.

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