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Comparison of ventilatory modes to facilitate liberation from mechanical ventilation: protocol for a systematic review and network meta-analysis

Kimberley A Lewis,[1] Dipayan Chaudhuri,[1] Gordon Guyatt,[1,2] Karen E A Burns,[3] Karen Bosma,[4] Long Ge,[5] Tim Karachi,[1] Thomas Piraino,[3] Shannon M Fernando,[6] Nischal Ranganath,[1] Laurent Brochard,[3] Bram Rochwerg[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Bram Rochwerg;
rochwerg@mcmaster.ca

ABSTRACT

Introduction Timely liberation from invasive mechanical ventilation is important to reduce the risk of ventilator-associated complications. Once a patient is deemed ready to tolerate a mode of partial ventilator assist, clinicians can use one of multiple ventilatory modes. Despite multiple trials, controversy regarding the optimal ventilator mode to facilitate liberation remains. Herein, we report the protocol for a systematic review and network meta-analysis comparing modes of ventilation to facilitate the liberation of a patient from invasive mechanical ventilation.

Methods and analysis We will search MEDLINE, EMBASE, PubMed, the Cochrane Library from inception to April 2019 for randomised trials that report on critically ill adults who have undergone invasive mechanical ventilation for at least 24 hours and have received any mode of assisted invasive mechanical ventilation compared with an alternative mode of assisted ventilation. Outcomes of interest will include: mortality, weaning success, weaning duration, duration of mechanical ventilation, duration of stay in the acute care setting and adverse events. Two reviewers will independently screen in two stages, first titles and abstracts, and then full texts, to identify eligible studies. Independently and in duplicate, two investigators will extract all data, and assess risk of bias in all eligible studies using the Modified Cochrane Risk of Bias tool. Reviewers will resolve disagreement by discussion and consultation with a third reviewer as necessary. Using a frequentist framework, we will perform random-effect network meta-analysis, including all ventilator modes in the same model. We will calculate direct and indirect estimates of treatment effect using a node-splitting procedure and report effect estimates using OR and 95% CI. We will assess certainty in effect estimates using Grading of Recommendations Assessment, Development and Evaluation methodology.

Ethics and dissemination Research ethics board approval is not necessary. The results will be disseminated through publication in a peer-reviewed journals.

PROSPERO registration number CRD42019137786

Strengths and limitations of this study

- This will be the first network meta-analysis conducted addressing this topic. Previous systematic reviews have combined various modalities of ventilator weaning providing only pairwise meta-analysis and not including indirect evidence.
- By conducting a network meta-analysis, we will include all the relevant evidence in the same analytical model and produce the most comprehensive effect estimates for each weaning mode.
- Other strengths of this protocol include a comprehensive search strategy of published and unpublished literature, a predefined subgroup analysis plan, and inclusion of Grading of Recommendations Assessment, Development and Evaluation methodology to assess certainty in network estimates of effect.
- Limitations to this protocol include the anticipated high clinical heterogeneity given the variation in weaning protocols, timing of randomisation relative to the Task Force stage of the liberation process, and reporting of outcome measures across trials even within a certain mode of weaning.

INTRODUCTION

The complications associated with invasive mechanical ventilation are well documented.[1–3] Morbidity including ventilator-associated pneumonia and airway trauma, and mortality accrues as the duration of mechanical ventilation increases.[2 3] Consequently, timely and safe liberation from invasive mechanical ventilation is important to patients and clinicians alike, and is a key research priority in critical care.[4 5] Clinicians aim to initiate the weaning process early to facilitate rapid liberation as 40%–50% of the time patients spend on invasive ventilation is dedicated to weaning.[1] Recognising when patients are ready to be separated from

invasive ventilation is challenging. Clinical recognition may be suboptimal as approximately 50% of patients who experience unplanned extubations require reintubation, suggesting that some patients are mechanically ventilated longer than necessary.[6]

There are six steps from the initiation to cessation of mechanical ventilation.[1] Stage 1 begins with the initiation of invasive mechanical ventilation to support the patient while the underlying cause of respiratory failure resolves. In the second stage, the treating physician has a clinical suspicion that the patient may be ready for liberation from mechanical ventilation. This suspicion or recognition of weaning readiness is based on the patient meeting clinical criteria such as improved oxygen requirements, stabilised vital signs and improvement in the underlying disease that resulted in the initiation of ventilator support in an intensive care unit (ICU).[1] Stage 3 involves active screening for weaning readiness using prespecified criteria, including but not limited to, the Rapid Shallow Breathing Index (RSBI). The RSBI is performed without any ventilatory support and is calculated as a ratio comparing frequency of breathing to tidal volume (f_b/V_t). An RSBI <105 suggests that the patient is ready to be weaned and should proceed to the next step.[7]

Depending on the clinical scenario, and especially in those who were only intubated briefly (eg, a surgical procedure), an immediate extubation attempt may be the next step for those that 'pass' a weaning screen. In those with a lower or indeterminate probability for success, and who have been intubated for longer, the next step includes a spontaneous breathing trial (SBT). The first SBT is important as it is, by definition, the first true weaning attempt. As its name suggests, an SBT is performed with a mode of ventilation or technique that allows for spontaneous breathing. SBTs are typically conducted by reducing inspiratory and/or expiratory assist for 30–120 min and assessing whether the patient can tolerate the increased work of breathing.[1] Considerable controversy exists regarding the optimal technique to use to conduct an SBT. Regardless of the technique used, an increase in respiratory rate, decrease in oxygen saturation, change in tidal volume, heart rate and/or blood pressure, patient anxiety or discomfort suggest a failed SBT.[1] Patients who pass an SBT are generally considered suitable for liberation from mechanical ventilation, at least from a respiratory point of view, although they still need to undergo a separate assessment of their airway to determine full readiness for extubation. Extubation or liberation is considered stage 5, while a potential need for reintubation is stage 6.[1]

If a patient is otherwise stable but does not tolerate an initial SBT, there are multiple ventilator modes and techniques that can be used to begin a more gradual, prolonged wean. Perhaps the most common approach is to gradually decrease ventilator support (eg, gradual reduction in pressure support (PS) or daily T-piece trials).[8 9] There is little clarity regarding the best strategy to use to liberate patients who fail multiple SBTs. Although PS is the most common mode used worldwide at this stage of mechanical ventilation, clinicians may use multiple other modes of partial ventilator assist such as synchronised intermittent mandatory ventilation (SIMV), continuous positive airway pressure (CPAP), adaptive support ventilation (ASV), airway pressure release ventilation (APRV), proportional assist ventilation (PAV) or neutrally adjusted ventilator assist (NAVA).[10–14]

Despite multiple randomised controlled trails (RCTs) and systematic reviews addressing strategies for this more prolonged and gradual wean, no consensus exists regarding the optimal ventilatory mode to use for weaning.[15–19] The American Thoracic Society guideline addressing liberation of patients from invasive mechanical ventilation provided a conditional recommendation for patients to be placed on a protocolised weaning schedule after 24 hours of invasive mechanical ventilation; however, the guideline did not advise on a specific mode for weaning.[20]

Prior systematic reviews and meta-analyses examining this question have combined heterogeneous interventions to allow for pairwise comparisons resulting in estimates of effect that are difficult to interpret.[16–18] Moreover, the advent of newer weaning techniques, such as PAV with load-adjustable gain factors (PAV+), NAVA or Intellivent and SmartCare, mandates assessment of the comparative efficacy of these newer techniques.[11–14] Table 1 summarises some of the ventilatory modes that have been used for gradual weaning. The lack of a network meta-analysis (NMA) on this topic means that no analysis has yet included all modes in the same analytical model thereby optimally addressing the relative effectiveness of those modes tested in RCTs.

Given the importance of liberation from mechanical ventilation, and the number of comparisons between different ventilator modes found in the trial data, we plan to conduct a systematic review and NMA in order to summarise the available evidence addressing the optimal mode of ventilation for weaning.

METHODS

We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement for reporting NMA.[21] The PRISMA-P checklist can be found in the online supplementary information.

Study selection

We will include studies if they meet the following criteria:

1. The study design was a parallel-group RCT.
2. The study population includes at least 80% critically ill adults (≥18 years old) admitted to the ICU who have been invasively mechanically ventilated for at least 24 hours, and are either part of the Wind Group no wean, 2 or 3, or the corresponding Task Force groups 2–4.[1 22]
3. The comparison must be between two or more assisted ventilator modes, including but not limited to: SIMV,

Table 1 Basic description of the different ventilatory modes[37]

Ventilatory mode	Acronym	Description
Proportional assist ventilation (aka proportional pressure support, PS)	PAV	– The PS varies with each cycle and is proportional to the effort of the patient.
PAV with load-adjustable gain factors	PAV+	– The PS varies with each cycle and is proportional to the effort of the patient, and will modify with changes in airway resistance, lung compliance, which are automatically measured at intervals.
SmartCare		– Automated system designed to guide the weaning process. – Enacts a weaning protocol in PS mode that aims to maintain comfortable respiration for patients through adaptation or reduction in PS.
Neutrally adjusted ventilator assist	NAVA	– The level of ventilatory assistance is proportional to the patient's efforts determined by diaphragmatic electromyogram signal.
Synchronised intermittent mandatory ventilation	SIMV	– The ventilator will deliver a set number of predetermined breaths, and the patient is allowed to take spontaneous breaths between the delivered breaths. – The ventilator will ensure that the patient is fully exhaled prior to delivering a set breath to reduce asynchrony between the ventilator and patient.
Adaptive support ventilation	ASV	– Allows delivery of breaths that may be assisted or controlled in order to achieve a certain minute ventilation target determined by the clinician. The ventilator will automatically adjust the inspiratory pressure, the inspiratory to expiratory ratio, and the respiratory rate.
INTELLiVENT-ASV	INTELLiVENT-ASV	– The clinician sets the desired end-tidal CO_2 and the desired SpO_2. The ventilator then screens for weaning readiness, performs SBTs and will progressively decreases pressure control and positive end-expiratory pressure.
Pressure support	PS	The patient initiates every breath and the ventilator delivers support with a preset pressure.
Airway pressure release ventilation	APRV	– Patients breath at an elevated CPAP level that allows periodic release times to facilitate CO_2 clearance. – Airway pressure is gradually reduced while the time at the high pressure in prolonged.

CPAP, continuous positive airway pressure; SBTs, spontaneous breathing trials.

PS, T-piece, PAV, PAV with load-adjustable gain factors (PAV+), NAVA, APRV, SmartCare, mandatory minute volume or ASV.

4. Reported outcomes include at least one of: mortality, weaning success (measured by ability to fully liberate from invasive mechanical ventilation without reintubation for 7 days, regardless of use of non-invasive positive pressure ventilation or Optiflow), weaning duration (measured in days, from first SBT (initiation of weaning) until patient is ready for extubation from invasive mechanical ventilation as defined by study authors), duration of mechanical ventilation from time of intubation, duration of acute care (including ICU stay and acute care hospital stay in days), use of non-invasive ventilation (including continuous CPAP or bilevel positive airway pressure) or Optiflow, adverse events (self extubation rate, ventilator associated pneumonia, arrhythmias or pneumothorax), type and cumulative amount of sedation required, the number of failed liberations from extubation (defined as requiring reintubation within 7 days from extubation or need for non-invasive positive pressure ventilation), time from randomisation to extubation/successful extubation, need for tracheostomy, Patient-Ventilator Asynchrony Index.

We will exclude the following:

1. Trials that only compare different techniques and modes of ventilation for conducting SBTs.
2. Study populations of tracheostomised patients.
3. Trails that randomise patients to RSBI versus no RSBI.
4. Trials that randomise patients to invasive mechanical ventilation weaning versus extubation to non-invasive ventilation.

Search strategy

We will search MEDLINE, EMBASE, PubMed and the Cochrane Library from inception to April 2019 without language restrictions. Please see the online supplementary information for the search strategy. We will update the search within 4 months of manuscript submission.

We will also search conference proceedings from four conferences (American Thoracic Society, Society of Critical Care Medicine, American College of Chest Physicians and the European Society of Intensive Care Medicine) within the past 3 years. Two reviewers will screen the titles and abstracts to identify articles for full review and then in the second stage, evaluate the full text for eligibility. In addition, reviewers will screen the reference list of review articles and previously published meta-analysis, use the PubMed-related articles search feature, and contact experts in the field to identify additional studies that were not captured in our initial search. Disagreement between reviewers after the full-text review will be resolved by discussion and consultation with a third reviewer as necessary.

Data extraction

Teams of two independent reviewers will extract data using piloted data abstraction forms. We will collect the baseline population demographics (age, sex, type of ICU, APACHE II (Acute Physiology, Age, Chronic Health Evaluation) score, duration of mechanical ventilation, reason for ICU admission, comorbidities (including respiratory diseases such as chronic obstructive pulmonary disease, asthma, interstitial lung disease, etc) as well as details of the weaning intervention, the comparator and the outcome data. We will contact study authors for missing study information or to resolve disagreements between reviewers where required.

Risk of bias assessment

Reviewers will assess the risk of bias (ROB) in duplicate and independently using the Modified Cochrane Risk of Bias tool.[23] We will place a judgement of low risk or probably low risk (bias is not present or unlikely to alter findings), or high risk or probably high risk (bias may alter the results) for each of the following items: sequence generation, allocation, concealment, blinding of participants and clinicians, blinding of outcome assessment, blinding of data collectors and data analysts, lost to follow-up and other (eg, intention-to-treat analysis, trial stopped early). The overall ROB for each included trial will be considered low if ROB is low or probably low in all domains, or high if the ROB was high or probably high in one or more domains. Reviewers will resolve disagreement by discussion and, if necessary, by consultation with a third reviewer.[24]

Statistical analysis

We will perform a series of conventional meta-analyses with a random-effects model for all direct comparisons, followed by a frequentist random-effects NMA to assess the relative effect of all interventions simultaneously. We chose the random-effects model a priori as it produces a more conservative CI in the setting of high heterogeneity. Random-effects model also takes into account variation in treatment effect beyond the play of chance, such as variation due to differences in study populations, settings and conduct to enhance external validity. We will evaluate heterogeneity in treatment effects for direct effects between studies using the Cochrane Q-test and the I^2 when at least two studies are available for a pairwise comparison.[25–27] We will report direct, indirect and NMA point estimates as OR and the corresponding 95% CI. For continuous outcomes, we will report mean difference with corresponding 95% CI. We will calculate the frequentist analogue of the surface under the cumulative ranking curve (SUCRA) for each treatment.[28] Based on the mean SUCRA values, we will draw a heat plot for all outcomes.[29] The transitivity assumption will be assessed by comparing the distribution of the population, the intervention and the methodological characteristics of the studies across treatment comparisons. To assess incoherence (inconsistency), we will fit both a consistency and an inconsistency model for each outcome and assess global incoherence for the entire network for each outcome using the random-effects design-by-treatment interaction model,[30] and then local incoherence for each comparison using the node-splitting model.[31]

In the case of sparse networks, random-effect models may unnecessarily increase imprecision in 95% CI, even when the direct and indirect estimates are coherent. In this circumstance, we will substitute fixed-effect analysis for the random effects.[32] All analyses will be performed using the package mvmeta and network in Stata/IC V.15.1 for Windows (StataCorp).[33]

Planned subgroup and sensitivity analysis

If sufficient data are available, we will plan for the following subgroup analysis using network meta-regression statistical technique:

- Medical versus surgical ICU population (surgery during the index hospitalisation).
- Protocolised versus non-protocolised weaning strategies.
- Shorter (<1 weeks) versus prolonged (>1 weeks) weaning.
- High ROB versus low ROB studies.
- Patients with hypercapnic respiratory failure versus any other cause of respiratory failure as the indication for endotracheal intubation and invasive mechanical ventilation.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence for each comparison.[34] Our certainty assessment will address the domains of RoB, imprecision, inconsistency (heterogeneity in estimates of effect across studies), indirectness (related to the question or due to intransitivity) and publication bias.[32 35] If there is significant incoherence between direct and indirect estimates, we will use the one with the higher certainty rather than the network estimate. Imprecision for each comparison will only be assessed at the NMA level and not at the level of the direct or indirect estimate. Publication

bias will be formally assessed for each direct comparison using the Egger's test for direct estimates when there is at least 10 studies.[36]

The certainty in indirect estimates will be inferred from examination of the dominant first-order connecting loops associated with the particular comparison and will be the lowest of the direct estimates contributing to the indirect comparison. If there are issues with intransitivity in the dominant first order loop (important differences between studies forming the indirect loop in regards to clinical or methodological characteristics), we will further lower the certainty in the indirect estimate. For certainty of NMA estimates, we will use the higher of the direct or indirect estimates (assuming they are coherent).

More or less preferred treatments

For the outcome weaning success, we have developed a system to summarise the results, establishing different groups of weaning modes (from the best to the worst groups) based on the effect estimates obtained from the NMA, their associated evidence certainty and their SUCRA (ranking) values. First, we plan to separate moderate-to-high quality (which we define as high certainty) and low-to-very-low (which we define as low certainty) bodies of evidence (based on GRADE). Then, within each group, we will separate ventilator modes based on the magnitude of effect estimates (ie, based on the relative improvements in weaning success), as follows: group (1) among the best modes, based on the effect estimates, these interventions are better than PS (which we designated our primary comparator for this exercise), group (2) inferior to the best but better than the worst modes: based on the effect estimates these modes are superior to PS, but inferior to modes from group (1) and group (3) among the worst modes: these modes were worse in effect estimates when compared with PS).

Patient and public involvement

We have not and will not involve new patients or the public in this protocol.

DISSEMINATION

We will aim to disseminate our study results through publication in a peer-reviewed journal.

DISCUSSION

Mechanical ventilation is one of the hallmarks of critical care.[3] Despite this, there is no consensus on the best mode to facilitate liberation of critically ill adults from the ventilator. With the advent of newer modes of ventilator weaning, and new technologies, a systematic review and NMA is necessary to summarise the existing evidence and provide some guidance to bedside clinicians regarding how best to wean critically ill patients requiring mechanical ventilation.

This will be the first NMA conducted addressing this topic. Previous systematic reviews have combined various different modalities of ventilator weaning providing only pairwise meta-analysis and not including indirect evidence.[16 17 19] By conducting an NMA, we will include all the relevant evidence in the same analytical model and produce the most comprehensive effect estimates for each weaning mode. Strengths of this protocol include a comprehensive search strategy of published and unpublished literature, a predefined subgroup analysis plan, and inclusion of GRADE methodology to assess certainty in network estimates of effect.

Limitations to this protocol include the anticipated high clinical heterogeneity given the variation in weaning protocols, timing of randomisation relative to the Task Force stage of the liberation process, and reporting of outcome measures across trials even within a certain mode of weaning. To address clinical heterogeneity, we will evaluate if anticipated heterogeneity translates into statistical heterogeneity. If it does, we will explore the heterogeneity through predefined subgroup analysis. If unexplained heterogeneity still exists, we will account for this inconsistency in our GRADE evaluation, which will be reflected in our conclusions. In order to address differences in reporting of outcome measures, we will create a data abstraction form a priori that will carefully consider the different ways that outcomes could be reported. This form will be pilot tested to ensure it is comprehensive and easy to use. In addition, we will be abstracting data in duplicate such that if there are discrepancies, we can address them through consensus, and potentially involving a third reviewer.

In conclusion, this protocol describes the details and methodology of a planned systematic review and NMA addressing the comparative efficacy of different ventilatory modes for weaning from invasive mechanical ventilation. The results of this NMA are expected to inform daily practice, clinical practice guidelines and guide areas of investigation for future RCTs.

Author affiliations
[1]Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[3]St Michael's Hospital, Toronto, Ontario, Canada
[4]London Health Sciences Centre, London, Ontario, Canada
[5]The First Clinical Medical College of Lanzhou University, Lanzhou, China
[6]Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada

Contributors BR, KAL and DC conceived the study. KAL, BR, DC, GG, LB, KEAB and KB contributed to protocol development. BR, DC and KAL drafted the protocol. KAL, DC, GG, KEAB, KB, LG, TK, TP, SMF, NR, LB and BR contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As this is a protocol for a systematic review of already published literature, research ethics board approval will not need for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

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