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Brain Natriuretic Peptide to Predict Successful Extubation in Critically Ill Patients: Protocol for a Systematic Review and Meta-Analysis.

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Keywords:	Natriuretic Peptide, Brain, Respiration, Artificial, Ventilator Weaning, Intensive Care, INTENSIVE & CRITICAL CARE

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Manuscripts

Brain Natriuretic Peptide to Predict Successful Extubation in Critically Ill Patients: Protocol for a Systematic Review and Meta-Analysis.

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Abstract

Introduction

Predicting successful extubation among critically ill patients receiving mechanical ventilation can be challenging. The current parameters used to predict successful extubation have shown variable predictive value. Extubation failure has consistently been shown to portend greater risk of complications. Brain natriuretic peptide (BNP) has been proposed as a novel biomarker to help guide decision-making in readiness for extubation following a spontaneous breathing trial (SBT). Current evidence on the predictive ability of BNP have been uncertain, and as such, BNP has not been integrated in clinical practice guidelines (CPG).

Methods and analysis

We will perform a systematic review and meta-analysis to evaluate the value of BNP during SBT to predict extubation success in patients receiving mechanical ventilation. A search strategy will be developed in collaboration with a research librarian, and electronic databases (MEDLINE, EMBASE, Cochrane Library, Web of Science) and additional sources will be searched. Search themes will include: 1) brain natriuretic peptide, and 2) weaning, extubation, and/or liberation from mechanical ventilation. Citation screening, selection, quality assessment and data abstraction will be performed in duplicate. The primary outcome will be extubation failure as defined in each study; secondary outcomes will include time to reintubation, mortality, mechanical ventilation duration, total and post-extubation ICU stay, hospitalization duration, tracheostomy rate, ICU-acquired weakness rate, and ventilator free days. Primary statistical analysis will include predictive value of BNP by receiver operating characteristic (ROC) curve, sensitivity/specificity and likelihood ratios for the combination of BNP and conventional SBT parameters for extubation failure. Secondary statistical analysis will be performed on individual and combinations of extracted metrics.

Ethics and dissemination

Our study will add knowledge by mapping out the current body of evidence on the value of BNP testing for prediction of successful extubation, and describe knowledge gaps and research priorities. Research ethics approval is not required for this review.

Trial registration number

PROSPERO CRD42018087474

Keywords

Natriuretic Peptide, Brain; Respiration, Artificial; Ventilator Weaning; Intensive Care; Critical Care.

Strengths and limitations

Strengths

- Comprehensive search using a peer-reviewed research methodology designed by a research librarian.

Limitations

- Heterogeneity of BNP use and correlation to SBT success and rate of extubation may undermine our capacity to perform meta-analysis.
- Heterogeneity of causes for respiratory failure and intubation may dilute the predictive potential of BNP for successful liberation in our meta-analysis.
- Number of high quality studies may be low, which would impact the confidence of the recommendations that could be derived.

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Introduction

Description of the condition

Predicting successful extubation among critically ill patients receiving mechanical ventilation can be challenging, and there are no standardized methods for assessing readiness for extubation (1). The most common approach to assessing readiness is a spontaneous breathing trial (SBT), in which the patient's ventilator support is decreased to at minimum, or completely suspended (i.e., "T-piece trial") (1,2). The American College of Chest Physicians/American Thoracic Society (ACCP/ATS) clinical practice guideline (CPG) on liberation from mechanical ventilation suggests a SBT with inspiratory pressure support as the preferred technique; however, it acknowledges the relatively limited evidence supporting a specific technique (1). Currently utilized clinical parameters following the performance of a SBT to guide decisions about extubation include changes to hemodynamic profile, work of breathing, respiratory rate, the rapid shallow breathing index (RSBI), and alterations to level of consciousness, amongst others. These parameters have shown variable value for predicting successful liberation from mechanical ventilation (3-5). Brain Natriuretic Peptides (BNP) has been proposed as a novel biomarker to help guide decision-making for readiness for extubation following a SBT. To date, clinical practice guidelines have not specifically integrated evidence from studies evaluating BNP to predict successful liberation from mechanical ventilation.

Description of the intervention

BNP is a sensitive marker of myocardial stretch, and its relative change in mechanically ventilated patients during a SBT has been proposed to provide incremental value for predicting successful extubation and liberation from mechanical ventilation (4,6,7). BNP is a natriuretic peptide released from cardiomyocytes. Available assays currently detect an inert 76 amino acid N-terminal-pro-BNP (NT-proBNP), or the 32 amino acid active form, BNP, cleaved from NT-proBNP, which has natriuretic, diuretic and hemodynamic properties. The half-life is estimated to be 20 minutes, so assessing variation within the limits of a SBT is biologically plausible (5). The majority of clinical evidence has evaluated the utility of BNP in the context of the diagnosis, prognosis and management of heart failure. Several studies have implied subclinical congestion and overt pulmonary edema due to changes in left ventricular afterload changes may be common among patients during a SBT and may be readily detected by measuring relative changes in BNP (8-12).

Why is it important to do this review?

While a number of studies have described BNP measurement during weaning from mechanical ventilation among critically ill patients, interpretation is challenging due to considerable variation in study design, case mix, heterogeneity in BNP measurement, and SBT definitions and protocols. However, extubation failure has consistently been shown to portend greater risk of complications including reintubation (13), nosocomial pneumonia, mortality, and prolongation in intensive care unit (ICU) stay (2,14,15). Successful liberation from mechanical ventilation has not been consistently or well-defined in the literature. The majority of studies and the ACCP/ATS CPG apply a definition of successful liberation as a patient not requiring re-inbutation or application of new non-invasive ventilation in the 48 hours following initial extubation (1). Development and validation of rigorous methods to improve clinician decision support and extubation success may improve patient outcomes, optimize resource use and inform about the contributing factors to extuation failure in selected clinical circumstances. Synthesis of the existing data in a systematic review and meta-analysis, along with providing evidence-based recommendations will contribute valuable insight for clinical practice in ICU settings, as well as guide future research in the field.

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Objectives

Our objective of this systematic review is to rigorously evaluate the value of BNP measurement during a SBT as a biomarker to predict extubation success among patients receiving mechanical ventilation. We hypothesize that BNP will add incremental predictive value for successful liberation from mechanical ventilation to standard clinical and biochemical parameters assessed during SBT.

Methods and analysis

Study design

We will perform a systematic review and meta-analysis using the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination (14), and according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) Guideline (16).

Study registration

The systematic review protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (http://ww.crd.york.ac.uk/prospero), and will be reported using PRISMA-P. Registration number #CRD42018087474 on 2018-02-06.

Ethics and dissemination

Data for this review will be sourced from available published and unpublished studies, if applicable. As such, no patient-specific primary data will be collected, and formal health research ethics approval is not required. Our study will be disseminated through a conventional peer-reviewed publication and presentation at a scientific congress. In addition, we will disseminate our findings regionally and nationally through the Canadian Critical Care Society and Alberta Health Services Critical Care Strategic Clinical Network (https://criticalcareresearchscn.com/public), along with novel dissemination strategies such as Twitter. If our protocol needs to be amended, the date, details of the change and the rationale will be documented in the revised protocol and updated on PROSPERO.

Patient and Public Involvement

Patients and public were not directly involved in the development of this study protocol. The research question and outcomes measures are related to patient' priorities and experiences as the goal of this study is to add knowledge in regards to ventilator weaning and prediction of extubation success which may have direct impact on patient's care (i.e success of extubation, ventilator days, rate of tracheostomy, mortality).

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomized and pseudo-randomized controlled trials that describe BNP levels during weaning from mechanical ventilation in respiratory failure patients. We will also include prospective observational studies that similarly describe BNP levels during weaning and association with re-intubation rates. We will exclude retrospective studies since the timing of BNP measurement relative to the timing of the SBT is of critical importance for this question, and may be highly prone to bias and inaccuracy. We will include studies reported as full text, published as an abstract only, and any relevant unpublished data obtained from the authors. There will be no language restrictions.

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Eligibility of Individual Studies

Inclusion criteria will include studies with patients receiving invasive mechanical ventilation without age restriction in whom a weaning trial was performed, and BNP levels were measured within 6h of SBT cessation. We will exclude studies with insufficient data for the outcomes measured if we are unable to obtain the necessary original data from the primary authors.

Search methods

The search strategy will be developed and executed by an research librarian and will be peer-reviewed by a second research librarian(17-21). We will search electronic databases: Ovid MEDLINE (1946-); Ovid EMBASE (1974-); Wiley Cochrane Library (inception-), including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL); and Web of Science Core Collection via Clarivate Analytics (1900-). A combination of the following search themes will be used: 1) brain natriuretic peptide, any subtype, and 2) weaning, extubation, or liberation from mechanical ventilation. Results will be limited to human studies, published in any language from database inception. Bibliographic records will be exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database duplicate removal and screening. See Appendix for the Medline strategy.

Additional sources will be included in the search strategy. The cited and citing references of included studies and relevant review articles will be screened. We will also search trial registry records via ClinicalTrials.gov, and meeting abstracts via the Conference Proceedings Citation Index (Clarivate Analytics). Finally, we will identify relevant clinical guidelines by searching Choosing Wisely Canada, the National Guidelines Clearinghouse, and TRIP (Turning Research Into Practice) Database.

Studies assessment

Study selection

Eligible articles will be identified through two phases. In the first phase, two authors will independently review the titles and abstracts of all retrieved bibliographic records using EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) for potential inclusion. In the second phase, full texts of the selected articles will be retrieved and two authors will independently review and select studies that meet the inclusion criteria.

Data extraction

For full-text studies selected for inclusion, relevant information will be abstracted using piloted and standardized electronic data forms by the same two authors independently. Abstracted data will be then compared between the two authors. Disagreements at every step will be resolved through discussion. In the case of unresolved matters, a third author (SMB) will be involved.

Data extracted will include study features, patient characteristics (e.g., age, sex, comorbid disease, organ failure scores, acuity of illness scores, case-mix and diagnostic classification, fluid balance), transthoracic echocardiography parameters, duration of mechanical ventilation, type of and duration of SBT, ventilator parameters at end of SBT, percentage of successful SBT, rate of reintubation, type of BNP, BNP difference pre/post weaning trial, relative BNP change pre/post weaning trial, BNP difference pre/post weaning trial for extubation failure, relative BNP change pre/post weaning trial for extubation failure. Likelihood ratios, predictive values, sensitivity/specificity and area under curve (AUC) for rate of extubation failure or rate of reintubation will be extracted when available.

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Method for missing data

We will contact study authors for relevant missing data in aggregate form. If supplementary data is provided in non-aggregate form, we will perform relevant statistical analysis.

Data analysis and synthesis

The primary endpoint will be extubation failure, as defined in each study. Secondary endpoints will include time to reintubation; mortality; duration of mechanical ventilation; total and post-extubation ICU stay; duration of hospitalization; rate of tracheostomy; rate of ICU-acquired weakness; and ventilator free days. Primary statistical analysis will include predictive value of BNP by standard receiver-operator characteristic (ROC) curve, sensitivity/specificity, and likelihood ratios for the combination of BNP gradient AND SBT for extubation failure. Because some studies may have utilized different BNP assessment protocols, we will also secondarily assess the predictive value, sensitivity/specificity and likelihood ratios of: 1) combination of BNP pre-SBT AND SBT, 2) combination of BNP post-SBT AND SBT, 3) BNP gradient alone, or 4) SBT alone for extubation failure. To further characterize the net effect of reclassification of BNP upon standard SBT endpoints (such as RSBI), a net reclassification index (NRI/IDI) will be used.

Descriptive analyses will be performed on all articles. Should a sufficient number of studies sharing designs and measurement of comparators be available (3 or more), we will perform pooled meta-analyses of the aforementioned primary and secondary endpoints.

Sensitivity analyses in predefined populations will include: patients intubated for reasons other than respiratory failure (e.g., elective pre-operative but unable to extubate), patients with respiratory failure from cardiac causes, post-cardiac surgery, with acute respiratory distress syndrome, and with sepsis.

Quality assessment of primary studies

Quality of each study will be independently analyzed by two authors using the QUADAS-2 questionnaire for systematic reviews (22). Seven parameters (patient selection bias, patient selection applicability, index test (BNP) risk of bias, index test applicability, reference test (SBT) risk of bias, and risk of bias due to timing) will be scored on a scale from 1-3; 1 for low risk of bias, 2 for moderate and 3 for high risk for bias. Scores will be averaged between the two reviewers. A score of 7-10 will be qualified as high quality, 11-14 as intermediate and >14 as low quality. To assess for bias or systematic heterogeneity, a visual inspection of a funnel plot will be utilized.

Quality assessment of the body of knowledge

We will assess the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (23). This will be performed in duplicate by two independent reviewers. We will present the results of the review in the “Summary of Findings” tables.

Discussion

General

The role of BNP as an additional predictor to SBT for successful extubation is an innovative development, particularly within the context of difficulty with the currently available methods. The sensitivity of BNP for changes in cardiac stress and loading makes its predictive ability for significant clinical outcomes in non-cardiac pulmonary conditions unclear. Current studies evaluating BNP are variable. Our systematic review and meta-analysis will add new knowledge by mapping out the current body of evidence on the value of BNP testing to guide clinicians about decision-making on the timing of extubation for mechanically ventilated patients, along with further describe existing knowledge gaps and identification of research

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priorities. The key strength of the protocol is its comprehensive search for relevant studies including ongoing trials and unpublished data and rigorous methodology.

Expected limitations

There are potential limitations to our review. First, the heterogeneity of methods by which BNP is used and correlated to SBT success and rate of extubation may undermine our capacity to perform meta-analysis. Second, the heterogeneity of causes for respiratory failure and intubation may dilute the predictive potential of BNP for successful liberation in our meta-analysis. Third, given this is a relatively new application of such a method, the number of high quality studies may be low, which would impact the confidence of the recommendations that could be derived.

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Contributors

JD and JW were responsible for the preparation of the protocol and manuscript preparation. SMB, JS, JD and JW were responsible for finalizing the protocol, statistical methods, and completion of the final manuscript. RF developed the search strategy and conducted the search in consultation with JD, JW and SMB. MS provided support for methodology. BV provided support for statistical analysis. SMB conceived the project, and all authors provided critical revision of the protocol and final manuscript. SMB will guarantee the content of the review. All Authors read and approved the final manuscript.

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Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed.

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Supplementary material

Appendix 1: PRISMA-P 2015 checklist (16)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Appendix 2: Search Strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Strategy:

1 Biomarkers/bl [blood] (98759)
2 Natriuretic Peptide, Brain/ (12407)
3 Nerve Tissue Proteins/ (82365)
4 Peptide Fragments/bl [blood] (9649)
5 ((biomarker* or marker*) adj2 (myocardial adj1 (strain* or stretch*))).tw,kf. (15)
6 ((biomarker* or marker*) and (PVR or vascular resistance*)).tw,kf. (846)
7 ((biomarker* or marker*) and (RV strain* or ventricular strain*)).tw,kf. (73)
8 BNP*.tw,kf. (9471)
9 (NT-proBNP* or NTproBNP*).tw,kf. (5278)
10 N terminal proBNP*.tw,kf. (251)
11 natriuretic peptide*.tw,kf. (26604)
12 nerve tissue protein*.tw,kf. (150)
13 or/1-12 [Combined MeSH & text words for BNP] (210406)
14 Ventilator Weaning/ (3444)
15 (extubat* adj2 (fail* or succe* or unsuccessful*)).tw,kf. (1436)
16 CPAP trial*.tw,kf. (59)
17 (pressure support ventilation adj3 trial*).tw,kf. (12)
18 SBT*.tw,kf. (2697)
19 (spontaneous breathing adj3 trial*).tw,kf. (485)
20 ((T-piece* or T-tube*) adj3 trial*).tw,kf. (103)
21 or/14-20 [Combined MeSH & text words for breathing trials] (7134)
22 Airway Management/ (2129)
23 Respiration, Artificial/ (44154)
24 ((airway* or air way*) adj3 (control* or manage*)).tw,kf. (9111)
25 ((artificial* or mechanical*) adj1 (respir* or ventilat*)).tw,kf. (51467)
26 respirator*.tw,kf. (387837)
27 ventilator*.tw,kf. (47662)
28 or/22-27 [Combined MeSH & text words for artificial respiration] (465447)
29 Airway Extubation/ (923)
30 Tidal Volume/ (9135)
31 extubat*.tw,kf. (11474)
32 liberat*.tw,kf. (22840)
33 postextubat*.tw,kf. (490)
34 tidal volume*.tw,kf. (13308)
35 wean*.tw,kf. (42743)
36 or/29-35 [Combined text words for weaning] (92605)
37 and/28,36 [Combined concept for weaning from artificial respiration] (24471)
38 or/21,37 [Combined concepts for breathing trials or weaning from artificial respiration] (28432)
39 and/13,38 [Combined index test & condition concepts] (186)
40 exp Animals/ not Humans/ (4428797)
41 (animal model* or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or hamster* or horses or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or rodent* or sheep or simian or sow or sows or vertebrate or vertebrates).ti. (2162123)
42 39 not (40 or 41) [Excluded animal studies] (155)
43 remove duplicates from 42 (155)

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Appendix 3: Data extraction parameters

Authors (first two)
Title
Journal
Year
DOI
Library
PMID
PDF availability
Setting
Academic setting
Age range
% males
Weight
Height
BMI
EF
Diastolic function (presence, severity)
Valvular dysfunction (type, severity)
Organ failure scores
Acuity of illness scores
Fluid balance at time of SBT
Atrial fibrillation
Pulmonary emboli
Pulmonary hypertension
Chronic kidney disease
Renal replacement therapy
Diagnosis
Intubation status
Duration of intubation
SBT type
Duration of SBT
Respiratory Rate at end of SBT
PS at end of SBT
PEEP at end of SBT
PaO2/FiO2
% Successful SBT
% failure extubation
Time to reintubation
Ventilator free days
Mortality at 30 days
Total ICU admission days
Post-extubation ICU days
Hospitalization days
% Tracheostomy
ICU-acquired weakness rate
BNP type
BNP pre-SBT
BNP post-SBT
% BNP change

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Appendix 4: QUADAS-2 Checklist (22)

QUADAS-2

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- Was a case-control design avoided? Yes/No/Unclear
- Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? CONCERN: LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
- If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

- Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
- Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

- Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- Did all patients receive a reference standard? Yes/No/Unclear
- Did patients receive the same reference standard? Yes/No/Unclear
- Were all patients included in the analysis? Yes/No/Unclear

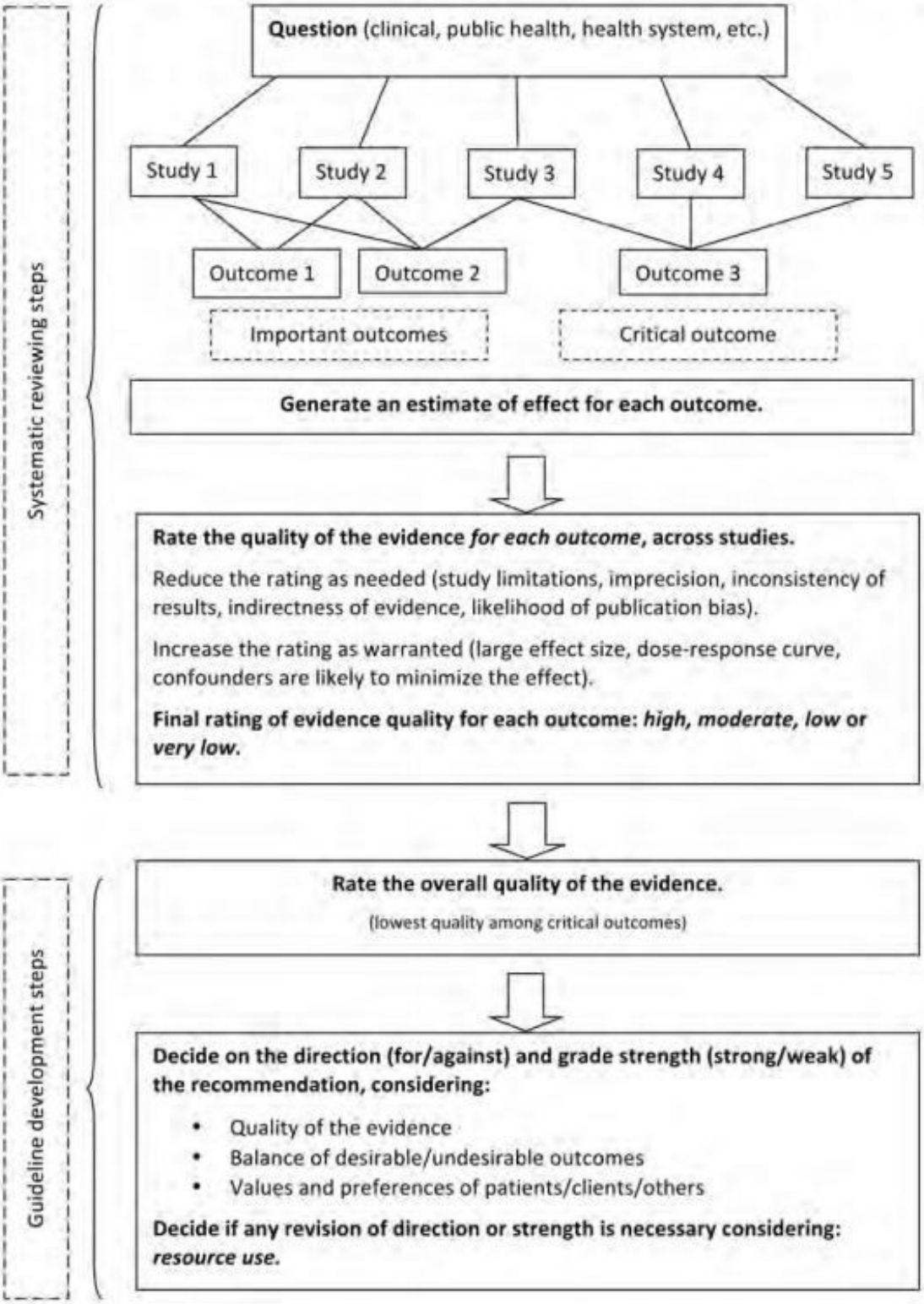
Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

Appendix 5: Grading of Recommendations Assessment, Development and Evaluation (23)

The scoring system used for *Clinical Evidence* reviews

Type of evidence		
Initial score based on type of evidence	+4	RCTs/ SR of RCTs, +/– other types of evidence
	+2	Observational evidence (e.g., cohort, case-control)
Quality		
Based on	Blinding and allocation process	
	Follow-up and withdrawals	
	Sparse data	
	Other methodological concerns (e.g., incomplete reporting, subjective outcomes)	
Score	0	No problems
	–1	Problem with 1 element
	–2	Problem with 2 elements
	–3	Problem with 3 or more elements
Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies (or inconsistency across studies is explained by a dose response); also 1 point added if adjustment for confounders would have increased the effect size
	0	All/most studies show similar results
	–1	Lack of agreement between studies (e.g., statistical heterogeneity between RCTs, conflicting results)
Directness		
Based on	The generalisability of population and outcomes from each study to our population of interest	
Score	0	Population and outcomes broadly generalisable
	–1	Problem with 1 element
	–2	Problem with 2 or more elements
Effect size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyses included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant

Figure 1. Overview of the GRADE process (modified from Guyatt et al.[8])



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Brain Natriuretic Peptide to Predict Successful Liberation from Mechanical Ventilation in Critically Ill Patients: Protocol for a Systematic Review and Meta-Analysis.

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Natriuretic Peptide, Brain, Respiration, Artificial, Ventilator Weaning, Intensive Care, INTENSIVE & CRITICAL CARE

SCHOLARONE™
Manuscripts

Brain Natriuretic Peptide to Predict Successful Liberation from Mechanical Ventilation in Critically Ill Patients: Protocol for a Systematic Review and Meta-Analysis.

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Abstract

Introduction

Predicting successful liberation from mechanical ventilation (MV) among critically ill patients receiving MV can be challenging. The current parameters used to predict successful extubation have shown variable predictive value. Brain natriuretic peptide (BNP) has been proposed as a novel biomarker to help guide decision-making in readiness for liberation of MV following a spontaneous breathing trial (SBT). Current evidence on the predictive ability of BNP has been uncertain, and BNP has not been integrated in clinical practice guidelines (CPG).

Methods and analysis

We will perform a systematic review and meta-analysis to evaluate the value of BNP during SBT to predict success of liberation from MV. A search strategy will be developed in collaboration with a research librarian, and electronic databases (MEDLINE, EMBASE, Cochrane Library, Web of Science) and additional sources will be searched. Search themes will include: 1) brain natriuretic peptide, and 2) weaning, extubation, and/or liberation from MV. Citation screening, selection, quality assessment and data abstraction will be performed in duplicate. The primary outcome will be liberation from MV; secondary outcomes will include time to reintubation, mortality, MV duration, total and post-extubation ICU stay, hospitalization duration, tracheostomy rate, ICU-acquired weakness rate, and ventilator-free days. Primary statistical analysis will include predictive value of BNP by receiver operating characteristic (ROC) curve, sensitivity/specificity and likelihood ratios for combination of BNP and SBT parameters for failure of liberation from MV. Secondary statistical analysis will be performed on individual and combinations of extracted metrics.

Ethics and dissemination

Our review will add knowledge by mapping the current body of evidence on the value of BNP testing for prediction of successful liberation from MV, and describe knowledge gaps and research priorities. Our findings will be disseminated through peer-reviewed publication, presentation at a scientific congress, through regional/national organizations and social media. Research ethics approval is not required.

Trial registration number

PROSPERO CRD42018087474

Keywords

Natriuretic Peptide, Brain; Respiration, Artificial; Ventilator Weaning; Intensive Care; Critical Care.

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Strengths and limitations

Strengths

- Rigorous and comprehensive search strategy using a peer-reviewed research methodology designed in consultation with a research librarian.

Limitations

- Heterogeneity of BNP use in clinical practice and correlation to SBT success and rate of liberation from MV may undermine the capacity to perform meta-analysis.
- Heterogeneity of causes for respiratory failure and intubation may dilute the predictive potential of BNP for successful liberation in our meta-analysis.
- Number of high quality studies may be low, which would impact the confidence of the recommendations that could be derived.

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Introduction

Description of the condition

Predicting successful liberation from mechanical ventilation (MV) among critically ill patients can be challenging, and there are no standardized methods for assessing readiness for extubation (1). The most common approach to assessing readiness is a spontaneous breathing trial (SBT), in which the patient's ventilator support is decreased to at minimum, or completely suspended (i.e., "T-piece trial") (1,2). The American College of Chest Physicians/American Thoracic Society (ACCP/ATS) clinical practice guideline (CPG) on liberation from MV suggests a SBT with inspiratory pressure support as the preferred technique; however, it acknowledges the relatively limited evidence supporting a specific technique (1). Currently utilized clinical parameters following the performance of a SBT to guide decisions about extubation include changes to hemodynamic profile, work of breathing, respiratory rate, the rapid shallow breathing index (RSBI), and alterations to level of consciousness, amongst others. These parameters have shown variable value for predicting successful liberation from MV (3-5). Brain Natriuretic Peptides (BNP) has been proposed as a novel biomarker to help guide decision-making for readiness for liberation from MV following a SBT. To date, clinical practice guidelines have not specifically integrated evidence from studies evaluating BNP to predict successful liberation from MV.

Description of the intervention

BNP is a sensitive marker of myocardial stretch, and its relative change in patients receiving mechanical ventilation during a SBT has been proposed to provide incremental value for predicting successful liberation from MV (4,6,7). BNP is a natriuretic peptide released from cardiomyocytes. Available assays currently detect an inert 76 amino acid N-terminal-pro-BNP (NT-proBNP), or the 32 amino acid active form, BNP, cleaved from NT-proBNP, which has natriuretic, diuretic and hemodynamic properties. The half-life of BNP is estimated to be 20 minutes, while the half-life of NT-proBNP is estimated at 120 minutes, so assessing variation within the limits of a SBT is biologically plausible (5). The majority of clinical evidence has evaluated the utility of BNP in the context of the diagnosis, prognosis and management of heart failure. Several studies have implied subclinical congestion and overt pulmonary edema due to changes in left ventricular afterload changes may be common among patients during a SBT and may be readily detected by measuring relative changes in BNP (8-12). For the purpose of this systematic review, the term BNP will be used to refer to all forms of assays used in measurements of the various forms of the protein.

Why is it important to do this review?

While a number of studies have described BNP measurement during weaning from MV among critically ill patients, interpretation is challenging due to considerable variation in study design, case mix, heterogeneity in BNP measurement, and SBT definitions and protocols. However, extubation failure has consistently been shown to portend greater risk of complications including reintubation (13), nosocomial pneumonia, mortality, and prolongation in intensive care unit (ICU) stay (2,14,15). Successful liberation from MV has not been consistently or well-defined in the literature. The majority of studies and the ACCP/ATS CPG apply a definition of successful liberation as a patient not requiring re-inbutation or application of new non-invasive ventilation in the 48 hours following initial extubation (1). Development and validation of rigorous methods to improve clinician decision support and successful liberation from MV may improve patient outcomes, optimize resource use and inform about the contributing factors to extuation failure in selected clinical circumstances. Synthesis of the existing data in a systematic review and meta-analysis, along with providing evidence-based recommendations will contribute valuable insight for clinical practice in ICU settings, as well as guide future research in the field.

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Objectives

Our objective of this systematic review is to rigorously evaluate the value of BNP measurement with a SBT as a biomarker to predict liberation from MV among patients receiving MV. We hypothesize that BNP will add incremental predictive value for successful liberation from MV to standard clinical and biochemical parameters assessed during SBT.

Methods and analysis

Study design

We will perform a systematic review and meta-analysis using the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination (14), and according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) Guideline (Appendix 1) (16).

Study registration

The systematic review protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (http://ww.crd.york.ac.uk/prospero), and will be reported using PRISMA-P. Registration number CRD42018087474 on 2018-02-06.

Ethics and dissemination

Data for this review will be sourced from available published and unpublished studies, if applicable. As such, no patient-specific primary data will be collected, and formal health research ethics approval is not required. Our study will be disseminated through a conventional peer-reviewed publication and presentation at a scientific congress. In addition, we will disseminate our findings regionally and nationally through the Canadian Critical Care Society and Alberta Health Services Critical Care Strategic Clinical Network (https://criticalcareresearchscn.com/public), along with novel dissemination strategies on social medial (i.e., Twitter). If our protocol required amendment, the date, details of the change and the rationale will be documented in the revised protocol and updated on PROSPERO.

Patient and Public Involvement

Patients and public were not directly involved in the development of this study protocol. The research question and outcomes measures; however, are related to patient' priorities and experiences, as the goal of this study is to add knowledge in regards to mechanical ventilator liberation, which certainly has direct impact on patient's care (i.e., success of liberation, ventilator-free days, tracheostomy use, mortality).

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomized and pseudo-randomized controlled trials (as defined by as controlled trials in which patients are randomized according to methods other than concealed random allocation) that describe BNP levels with a SBT from MV in patients with respiratory failure. We will also include prospective observational studies that similarly describe BNP levels with a SBT and association with re-intubation rates. We will exclude retrospective studies since the timing of BNP measurement relative to the timing of the SBT is of critical importance for this question, and may be highly prone to bias and inaccuracy. We will include studies reported as full text, published as an abstract only, and any relevant unpublished data obtained from the authors. There will be no language restrictions.

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Eligibility of Individual Studies

Inclusion criteria will include studies with patients receiving invasive MV without age restriction in whom an SBT was performed. We will include studies with BNP assay of any type (BNP, NT-proBNP, etc.), if performed, before, during, after, or any combination of these within 120 minutes of the SBT. The cutoff of 120 minutes is chosen to account for approximately 5 half-lives of BNP kinetic profile, which is the more rapidly-degraded biomarker. NT-proBNP is a precursor to BNP with a longer half-life, approximately 120 minutes, so the cutoff of 120 minutes before or after SBT should remain valid to identify a significant increase. We will include studies with SBT of any type. We will exclude studies with insufficient data for the outcomes measured if we are unable to obtain the necessary original data from the primary authors.

Search methods

The search strategy will be developed and executed by an research librarian and will be peer-reviewed by a second research librarian (Appendix 2) (17-21). We will search electronic databases: Ovid MEDLINE (1946-); Ovid EMBASE (1974-); Wiley Cochrane Library (inception-), including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL); and Web of Science Core Collection via Clarivate Analytics (1900-). A combination of the following search themes will be used: 1) brain natriuretic peptide, any subtype, and 2) weaning, extubation, or liberation from mechanical ventilation. Results will be limited to human studies, published in any language from database inception. Bibliographic records will be exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database duplicate removal and screening. See Appendix for the Medline strategy. Additional sources will be included in the search strategy. The cited and citing references of included studies and relevant review articles will be screened. We will also search trial registry records via ClinicalTrials.gov, and meeting abstracts via the Conference Proceedings Citation Index (Clarivate Analytics). Finally, we will identify relevant clinical guidelines by searching Choosing Wisely Canada, the National Guidelines Clearinghouse, and TRIP (Turning Research Into Practice) Database.

Studies assessment

Study selection

Eligible articles will be identified through two phases. In the first phase, two authors will independently review the titles and abstracts of all retrieved bibliographic records using EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) for potential inclusion. In the second phase, full texts of the selected articles will be retrieved and two authors will independently review and select studies that meet the inclusion criteria.

Data extraction

For full-text studies selected for inclusion, relevant information will be abstracted using piloted and standardized electronic data forms by the same two authors independently (Appendix 3). Abstracted data will be then compared between the two authors. Disagreements at every step will be resolved through discussion. In the case of unresolved matters, a third author (SMB) will be involved.

Data extracted will include study features, patient characteristics (e.g., age, sex, comorbid disease, organ failure scores, acuity of illness scores, case-mix and diagnostic classification, fluid balance), transthoracic echocardiography parameters, duration of MV, type of and duration of SBT, ventilator parameters at end of SBT, percentage of successful SBT, rate of reintubation, type of BNP, BNP difference pre/post/during SBT, relative BNP change pre/post/during SBT, BNP difference pre/post/during SBT for liberation of MV, relative BNP change pre/post/during SBT for liberation of MV. Likelihood ratios, predictive values, sensitivity/specificity and area under curve (AUC) for rate of failure of liberation of MV, rate of reintubation, and rate of non-invasive ventilation post-extubation will be extracted when available.

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Method for missing data

We will contact study authors for relevant missing data in aggregate form. If supplementary data is provided in non-aggregate form, we will perform relevant statistical analysis.

Data analysis and synthesis

The primary endpoint will be liberation of MV, as defined in each study. We will consider successful liberation of MV not requiring reintubation or application of new non-invasive ventilation in the 48 hours following initial extubation, but will analyze any additional data after 48 hours as available in studies. SBT success, as defined in each study, and data on criteria used to define it will be analyzed as available. Secondary endpoints will include re-intubation rate and time to reintubation; time to non-invasive ventilation; mortality; duration of MV; total and post-extubation ICU stay; duration of hospitalization; rate of tracheostomy; rate of ICU-acquired weakness; and ventilator-free days.

Primary statistical analysis will include predictive value of BNP by standard receiver-operator characteristic (ROC) curve, sensitivity/specificity, and likelihood ratios for the combination of BNP gradient AND SBT for failure of liberation of MV. Because some studies may have utilized different BNP assessment protocols, we will also secondarily assess the predictive value, sensitivity/specificity and likelihood ratios of: 1) combination of BNP pre-SBT AND SBT; 2) combination of BNP post-SBT AND SBT; 3) BNP gradient alone; or 4) SBT alone for failure of liberation from MV. To further characterize the net effect of reclassification of BNP upon standard SBT endpoints (such as RSBI), a net reclassification index (NRI/IDI) will be used. Both BNP and NT-proBNP will be included in an initial pooled analysis, with subsequent subgroup analysis separating BNP and NT-proBNP if there are sufficient numbers of studies.
Descriptive analyses will be performed on all articles. Should a sufficient number of studies sharing designs and measurement of comparators be available (3 or more), we will perform pooled meta-analyses of the aforementioned primary and secondary endpoints.
Sensitivity analyses in predefined subgroups will include: age (specific strata contingent on data available); sex; patients intubated for reasons other than respiratory failure (e.g., elective pre-operative but unable to extubate); patients with respiratory failure from cardiac causes, post-cardiac surgery, with acute respiratory distress syndrome, and with sepsis; subtypes of BNP; subtypes of SBT.

Quality assessment of primary studies

Quality of each study will be independently analyzed by two authors using the QUADAS-2 questionnaire for systematic reviews (Appendix 4) (22). Seven parameters (i.e., patient selection bias, patient selection applicability, index test (BNP) risk of bias, index test applicability, reference test (SBT) risk of bias, and risk of bias due to timing) will be scored on a scale from 1-3; 1 for low risk of bias, 2 for moderate and 3 for high risk for bias. Scores will be averaged between the two reviewers. A score of 7-10 will be qualified as high quality, 11-14 as intermediate and >14 as low quality. To assess for bias or systematic heterogeneity, a visual inspection of a funnel plot will be utilized.

Quality assessment of the body of knowledge

We will assess the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Appendix 5-6) (23). This will be performed in duplicate by two independent reviewers. We will present the results of the review in the “Summary of Findings” tables.

Discussion

General

The role of BNP as an additional predictor to SBT for liberation of MV is an innovative development, particularly within the context of difficulty with the currently available methods. The sensitivity of BNP for

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changes in cardiac stress and loading makes its predictive ability for significant clinical outcomes in non-cardiac pulmonary conditions unclear. Current studies evaluating BNP are variable. Our systematic review and meta-analysis will add new knowledge by mapping the current body of evidence on the value of BNP testing to guide clinicians about decision-making on the timing of attempt for liberation from mechanical ventilation, along with further describing existing knowledge gaps and identification of research priorities. The key strength of the protocol is its comprehensive search strategy for relevant studies, including ongoing trials and unpublished data, and our rigorous methodology.

Expected limitations

There are potential limitations to our review. First, the heterogeneity of methods by which BNP is measured, used and correlated to SBT success and rate of liberation from MV may undermine our capacity to perform pooled analysis. Second, the heterogeneity of causes for respiratory failure and intubation may dilute the predictive potential of BNP for successful liberation in our meta-analysis. Third, given this is a relatively new application of such a method, the number of high quality studies may be low, which would impact the confidence of the recommendations that could be derived.

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Contributors

JD and JW were responsible for the preparation of the protocol and manuscript preparation. SMB, JS, JD and JW were responsible for finalizing the protocol, statistical methods, and completion of the final manuscript. RF developed the search strategy and conducted the search in consultation with JD, JW and SMB. MS provided support for methodology. BV provided support for statistical analysis. SMB conceived the project, and all authors provided critical revision of the protocol and final manuscript. SMB will guarantee the content of the review. All Authors read and approved the final manuscript.

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Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed.

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Supplementary material

Appendix 1: PRISMA-P 2015 checklist (16)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Appendix 2: Search Strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Strategy:
1 Biomarkers/bl [blood] (98759)
2 Natriuretic Peptide, Brain/ (12407)
3 Nerve Tissue Proteins/ (82365)
4 Peptide Fragments/bl [blood] (9649)
5 ((biomarker* or marker*) adj2 (myocardial adj1 (strain* or stretch*))).tw,kf. (15)
6 ((biomarker* or marker*) and (PVR or vascular resistance*)).tw,kf. (846)
7 ((biomarker* or marker*) and (RV strain* or ventricular strain*)).tw,kf. (73)
8 BNP*.tw,kf. (9471)
9 (NT-proBNP* or NTproBNP*).tw,kf. (5278)
10 N terminal proBNP*.tw,kf. (251)
11 natriuretic peptide*.tw,kf. (26604)
12 nerve tissue protein*.tw,kf. (150)
13 or/1-12 [Combined MeSH & text words for BNP] (210406)
14 Ventilator Weaning/ (3444)
15 (extubat* adj2 (fail* or succe* or unsuccessful*)).tw,kf. (1436)
16 CPAP trial*.tw,kf. (59)
17 (pressure support ventilation adj3 trial*).tw,kf. (12)
18 SBT*.tw,kf. (2697)
19 (spontaneous breathing adj3 trial*).tw,kf. (485)
20 ((T-piece* or T-tube*) adj3 trial*).tw,kf. (103)
21 or/14-20 [Combined MeSH & text words for breathing trials] (7134)
22 Airway Management/ (2129)
23 Respiration, Artificial/ (44154)
24 ((airway* or air way*) adj3 (control* or manage*)).tw,kf. (9111)
25 ((artificial* or mechanical*) adj1 (respir* or ventilat*)).tw,kf. (51467)
26 respirator*.tw,kf. (387837)
27 ventilator*.tw,kf. (47662)
28 or/22-27 [Combined MeSH & text words for artificial respiration] (465447)
29 Airway Extubation/ (923)
30 Tidal Volume/ (9135)
31 extubat*.tw,kf. (11474)
32 liberat*.tw,kf. (22840)
33 postextubat*.tw,kf. (490)
34 tidal volume*.tw,kf. (13308)
35 wean*.tw,kf. (42743)
36 or/29-35 [Combined text words for weaning] (92605)
37 and/28,36 [Combined concept for weaning from artificial respiration] (24471)
38 or/21,37 [Combined concepts for breathing trials or weaning from artificial respiration] (28432)
39 and/13,38 [Combined index test & condition concepts] (186)
40 exp Animals/ not Humans/ (4428797)
41 (animal model* or bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or hamster* or horses or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or rodent* or sheep or simian or sow or sows or vertebrate or vertebrates).ti. (2162123)
42 39 not (40 or 41) [Excluded animal studies] (155)
43 remove duplicates from 42 (155)

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Appendix 3: Data extraction parameters

Authors (first two)
Title
Journal
Year
DOI
Library
PMID
PDF availability
Setting
Academic setting
Age range
% males
Weight
Height
BMI
EF
Diastolic function (presence, severity)
Valvular dysfunction (type, severity)
Organ failure scores
Acuity of illness scores
Fluid balance at time of SBT
Atrial fibrillation
Pulmonary emboli
Pulmonary hypertension
Chronic kidney disease
Renal replacement therapy
Diagnosis
Intubation status
Duration of intubation
SBT type
Duration of SBT
Respiratory Rate at end of SBT
PS at end of SBT
PEEP at end of SBT
PaO2/FiO2
% Successful SBT
% failure extubation
Time to reintubation
Ventilator free days
Mortality at 30 days
Total ICU admission days
Post-extubation ICU days
Hospitalization days
% Tracheostomy
ICU-acquired weakness rate
BNP type
BNP pre-SBT
BNP post-SBT
% BNP change

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Appendix 4: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) Tool Checklist (22) (available at: https://www.bristol.ac.uk/media-library/sites/quadas/migrated/documents/quadas2.pdf)

QUADAS-2

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- Was a case-control design avoided? Yes/No/Unclear
- Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? CONCERN: LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
- If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

- Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
- Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

- Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- Did all patients receive a reference standard? Yes/No/Unclear
- Did patients receive the same reference standard? Yes/No/Unclear
- Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

Appendix 5: Quality assessment criteria (23)

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

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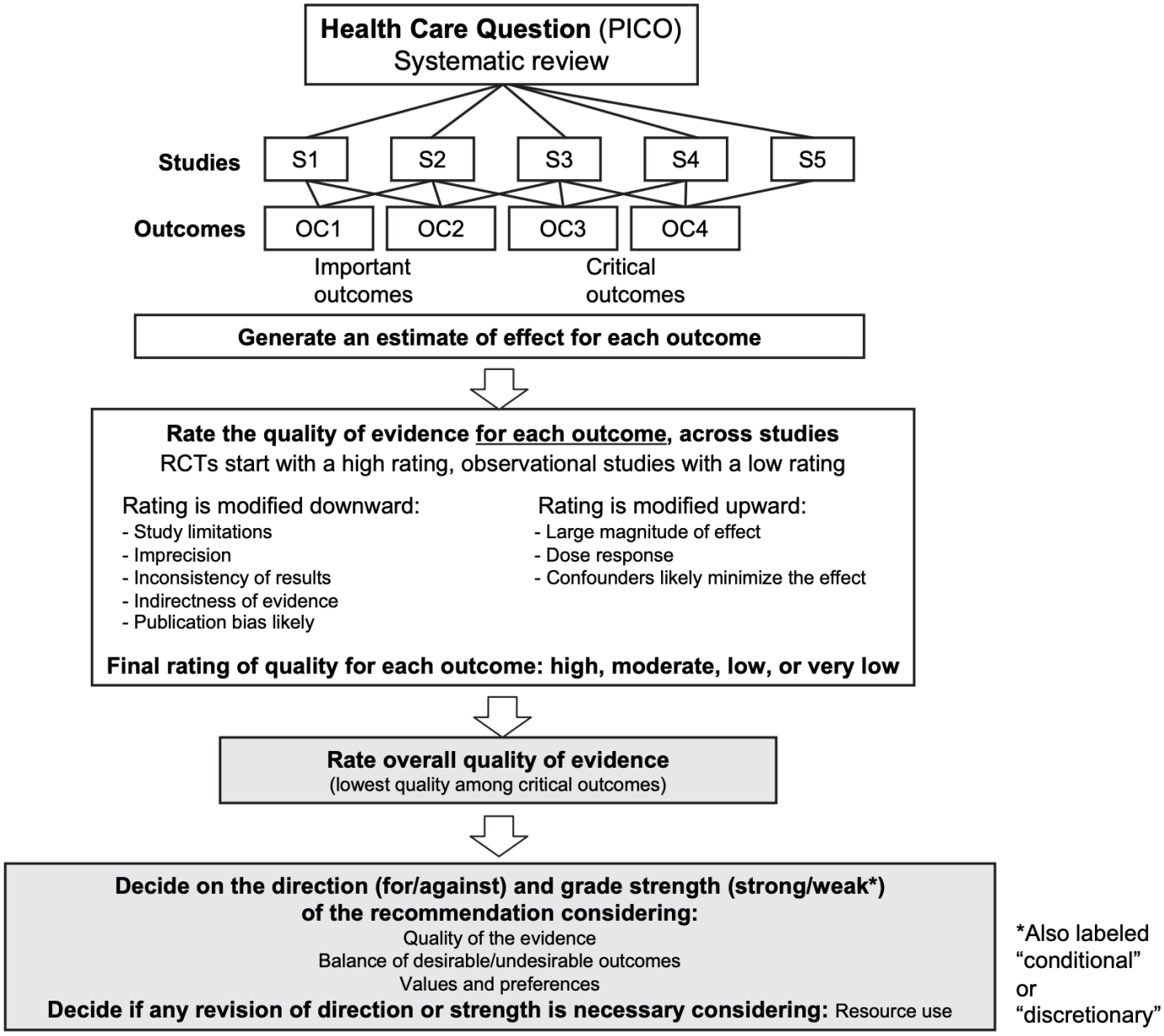
Appendix 6: Schematic view of GRADE's process for developing recommendations. (23)