

BMJ Open 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 into clinical practice guidelines.

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) BNP 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 postextubation intensive care unit (ICU) stay, hospitalisation duration, tracheostomy rate, ICU-acquired weakness rate and ventilator-free days. Primary statistical analysis will include predictive value of BNP by receiver operating characteristic 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 organisations and social media. Research ethics approval is not required.

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Strengths and limitations of this study

- Rigorous and comprehensive search strategy using a peer-reviewed research methodology designed in consultation with a research librarian.
- Heterogeneity of brain natriuretic peptide (BNP) use in clinical practice and correlation to spontaneous breathing trial success and rate of liberation from mechanical ventilation 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.

INTRODUCTION

Description of the condition

Predicting successful liberation from mechanical ventilation (MV) among critically ill patients can be challenging, and there are no standardised 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 (ie, '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 an SBT with inspiratory pressure support as the preferred technique; however, it acknowledges the relatively limited evidence supporting a specific technique.¹ Currently used clinical parameters following the performance of an SBT to guide decisions about extubation include changes to haemodynamic profile,

work of breathing, respiratory rate, the Rapid Shallow Breathing Index (RSBI) and alterations to level of consciousness, among others. These parameters have shown variable value for predicting successful liberation from MV.^{3–5} Brain natriuretic peptide (BNP) has been proposed as a novel biomarker to help guide decision-making for readiness for liberation from MV following an SBT. To date, CPGs 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 MV during an SBT has been proposed to provide incremental value for predicting successful liberation from MV.^{3–5} 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 haemodynamic properties. The half-life of BNP is estimated to be 20 min, while the half-life of NT-proBNP is estimated at 120 min, so assessing variation within the limits of an 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 oedema due to changes in left ventricular afterload changes may be common among patients during an SBT and may be readily detected by measuring relative changes in BNP.^{6–10} 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, casemix, heterogeneity in BNP measurement, and SBT definitions and protocols. However, extubation failure has consistently been shown to portend greater risk of complications including reintubation,¹¹ nosocomial pneumonia, mortality and prolongation in intensive care unit (ICU) stay.^{2 12 13} 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 reintubation 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, optimise resource use and inform about the contributing factors to extubation 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.

Objectives

Our objective of this systematic review is to rigorously evaluate the value of BNP measurement with an SBT as a biomarker to predict liberation from MV among patients receiving MV. We hypothesise 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,¹² and according to the Preferred Reporting Items for Systematic Review and Meta-analyses Protocol (PRISMA-P) guideline (see online supplementary appendix 1).¹⁴

Study registration

The systematic review protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/prospere/>), and will be reported using PRISMA-P.

Ethics and dissemination

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://criticalcarerearchscn.com/public>), along with novel dissemination strategies on social media (ie, Twitter). If our protocol requires 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 regard to mechanical ventilator liberation, which certainly has direct impact on patient's care (ie, success of liberation, ventilator-free days, tracheostomy use, mortality).

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised and pseudo-randomised controlled trials (as defined by as controlled trials in which patients are randomised according to methods other than concealed random allocation) that

describe BNP levels with an SBT from MV in patients with respiratory failure. We will also include prospective observational studies that similarly describe BNP levels with an SBT and association with reintubation 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.

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 min of the SBT. The cut-off of 120 min is chosen to account for approximately five 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 min, so the cut-off of 120 min 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 a research librarian and will be peer reviewed by a second research librarian (see online supplementary appendix 2).^{15–19} 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 and Web of Science Core Collection via Clarivate Analytics (1900-). A combination of the following search themes will be used: (1) BNP, any subtype and (2) weaning, extubation or liberation from MV. Results will be limited to human studies, published in any language from database inception. Bibliographic records will be exported to an EndNote V.X7 (Thomson Reuters, Philadelphia, Pennsylvania, USA) database duplicate removal and screening. See online supplementary 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 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 V.X7 (Thomson Reuters) 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 standardised electronic data forms by the same two authors independently (see online supplementary 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 (eg, age, sex, comorbid disease, organ failure scores, acuity of illness scores, casemix 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 for rate of failure of liberation of MV, rate of reintubation and rate of non-invasive ventilation postextubation will be extracted when available.

Method for missing data

We will contact study authors for relevant missing data in aggregate form. If supplementary data are 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 analyse 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 analysed as available. Secondary endpoints will include reintubation rate and time to reintubation; time to non-invasive ventilation; mortality; duration of MV; total and postextubation ICU stay; duration of hospitalisation; rate of tracheostomy; rate of ICU-acquired weakness and ventilator-free days.

Primary statistical analysis will include predictive value of BNP by standard receiver operating characteristic

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 used 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 characterise the net effect of reclassification of BNP on standard SBT endpoints (such as RSBI), a Net Reclassification Index/Integrated Discrimination Index 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 (three 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 (eg, elective preoperative 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 analysed by two authors using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) questionnaire for systematic reviews (see online supplementary appendix 4).²⁰ Seven parameters (ie, 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 to 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 used.

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 (see online supplementary appendices 5 and 6).²¹ 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 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 MV, 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 finalising 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.

Patient consent for publication Not required.

Ethics approval 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.

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REFERENCES

1. Ouellette DR, Patel S, Girard TD, *et al.* Liberation From Mechanical Ventilation in Critically Ill Adults: An Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline: Inspiratory Pressure Augmentation During Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Noninvasive Ventilation Immediately After Extubation. *Chest* 2017;151:166–80.
2. Boles JM, Bion J, Connors A, *et al.* Weaning from mechanical ventilation. *Eur Respir J* 2007;29:1033–56.
3. Zapata L, Vera P, Roglan A, *et al.* B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. *Intensive Care Med* 2011;37:477–85.
4. Chien JY, Lin MS, Huang YC, *et al.* Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. *Crit Care Med* 2008;36:1421–6.
5. Mekontso-Dessap A, de Prost N, Girou E, *et al.* B-type natriuretic peptide and weaning from mechanical ventilation. *Intensive Care Med* 2006;32:1529–36.
6. Grüber MR, Wigger O, Berger D, *et al.* Basic concepts of heart-lung interactions during mechanical ventilation. *Swiss Med Wkly* 2017;147:w14491.
7. Vieillard-Baron A, Matthay M, Teboul JL, *et al.* Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. *Intensive Care Med* 2016;42:739–49.
8. Buda AJ, Pinsky MR, Ingels NB, *et al.* Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med* 1979;301:453–9.
9. Lemaire F, Teboul JL, Cinotti L, *et al.* Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988;69:171–9.
10. Capdevila X, Perrigault PF, Ramonatxo M, *et al.* Changes in breathing pattern and respiratory muscle performance parameters during difficult weaning. *Crit Care Med* 1998;26:79–87.
11. Menon N, Joffe AM, Deem S, *et al.* Occurrence and complications of tracheal reintubation in critically ill adults. *Respir Care* 2012;57:1555–63.
12. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186–92.
13. Thille AW, Harrois A, Schortgen F, *et al.* Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–8.
14. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
15. Alobaidi R, Morgan C, Basu RK, *et al.* Associations between fluid balance and outcomes in critically ill children: a protocol for a systematic review and meta-analysis. *Can J Kidney Health Dis* 2017;4:2054358117692560.
16. McGowan J, Sampson M, Salzwedel DM, *et al.* PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40–6.
17. Sampson M, McGowan J, Cogo E, *et al.* An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol* 2009;62:944–52.
18. Rewa OG, Villeneuve PM, Lachance P, *et al.* Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review. *Intensive Care Med* 2017;43:750–63.
19. Lachance P, Villeneuve PM, Wilson FP, *et al.* Impact of e-alert for detection of acute kidney injury on processes of care and outcomes: protocol for a systematic review and meta-analysis. *BMJ Open* 2016;6:e011152.
20. Whiting PF, Rutjes AW, Westwood ME, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
21. Schünemann HJ, Schünemann AH, Oxman AD, *et al.* Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336:1106–10.