The impact of patient-ventilator asynchrony in adult mechanically ventilated patients on outcomes A systematic review and meta-analysis V.2

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Version 2

Feb 24, 2021

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dx.doi.org/10.17504/protocols.io.bsqtndwn

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ABSTRACT

1.Background

Patients-ventilator asynchrony (PVA) is defined as a mismatch between the patient breathing efforts with a ventilator's breath delivery. (1) PVA is a common problem in mechanically ventilated patients, (2, 3) which could potentially induce the exhaustion of diaphragm and respiratory muscles and deliver high tidal volume to the lung leading to ventilator-induced lung injury (VILI). (4, 5)

The impact of PVA including an acute phase of mechanical ventilation on clinical outcomes was not similar across studies. Thille AW et al. reported that higher incidence of PVA was associated with longer duration of mechanical ventilation, while this was not associated with mortality. (2) Conversely, Blanch L et al. showed that ICU mortality of the patients with higher incidence of PVA was significantly higher than that with lower incidence of PVA. (6) Furthermore, to date, there is no systematic review regarding PVA in the acute phase of mechanical ventilation. Furthermore, although adjustment of sedatives or ventilator settings were thought to be effective for improving PVA, there is no definitive intervention for improving PVA without closed-loop-ventilation such as Neurally Adjusted Ventilatory Assist (NAVA) and Proportional Assist Ventilation (PAV) in the weaning phase of mechanical ventilation. (7, 8, 9)

Therefore, we will conduct this systematic review and meta-analysis to clarify the impact of PVA on specific clinical outcomes and the effect of interventions in order to improve PVA for mechanically ventilated patients in the acute phase of mechanical ventilation.

2.Review question

Part A. The impact of PVA on clinical outcomes

To clarify the impact of patient-ventilator asynchrony in adult mechanically ventilated patients in acute phase of mechanical ventilation on outcomes.

Part B. The impact of interventions for mechanically ventilated patients on PVA

To clarify the impact of interventions for adult mechanically ventilated patients in acute phase of mechanical ventilation on PVA.

3.Method

3.1.1 Types of study to be included

Part A. The impact of PVA on clinical outcomes

We will include published and unpublished observational studies and secondary analysis of randomized controlled trials (RCTs) including crossover trials, cluster-randomized trials, quasi-randomized trials.

We will include studies presented only in abstract or letter form, in any language, from any country and with any

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length of follow-up.

Part B. The impact of interventions for mechanically ventilated patients on PVA
We will include published and unpublished observational studies and randomized controlled trials (RCTs) including crossover trials, cluster-randomized trials, quasi-randomized trials.
We will include studies presented only in abstract or letter form, in any language, from any country and with any length of follow-up.

3.1.2 Participants

Inclusion criteria

Adults aged 18 years and older
We define “acute phase” as within 72 hrs of initiation of mechanical ventilation, as soon as patients were not able to trigger all ventilator breaths or using assist-control ventilation mode.
Patients who have received mechanical ventilation including acute phase of mechanical ventilation.

Exclusion criteria

We will exclude the studies which assess the effects of interventions of NAVA and PAV. We will also exclude patients with weaning phase of mechanical ventilation, post-operation, do-not-resuscitate orders, suspected bronchopleural fistula or air leaks, those admitted for organ donation, less than 18 years old, pregnant patients.

3.1.3 Exposure(s)/Intervention(s)

Part A. The impact of PVA on clinical outcomes
We will include studies that have evaluated whether the incidence of PVA defined as asynchrony index (AI) $\geq$ 10% or ineffective trigger index (ITI) $\geq$ 10% or higher index defined by the trialists is associated with clinical outcomes in the acute phase of mechanical ventilation.
AI is defined as the number of asynchronous breaths, according to each study, divided by the total number of breaths (both requested and delivered) multiplied by 100. (2)
ITI is defined as the number of ineffective triggered breaths divided by the total number of triggered and ineffectively triggered breaths multiplied by 100. (3)

Part B. The impact of interventions for mechanically ventilated patients on PVA
We will include studies that have evaluated the impact of interventions that possibly affect PVA including acute phase of mechanical ventilation.

3.1.4 Control(s)

Part A. The impact of PVA on clinical outcomes
asynchrony index (AI) < 10%, ineffective trigger index (ITI) < 10% or lower index defined by the study authors

Part B. The impact of interventions for mechanically ventilated patients on PVA
Patients who have been defined as a control by the study authors

3.2 Outcomes

Part A. The impact of PVA on clinical outcomes

3.2.1 Primary outcomes

We will assess the association between PVA as AI, ITI or index defined by the study authors, respectively, with the following outcomes.
1. Duration of mechanical ventilation
2. ICU mortality
3. Hospital mortality

3.2.2 Secondary outcomes

4. Rate of reintubation
5. Rate of tracheostomy
6. All adverse events (as defined by the study authors).

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3.2.3 summary of PVA defined by the study authors

We will summarize the results as the same type of PVA such as breathe stacking, auto-triggering or double triggering, etc.

Part B. Interventions for improving PVA

3.2.1 Primary outcomes

1. Incidence of PVA
2. Duration of mechanical ventilation

3.2.2 Secondary outcomes

3. ICU mortality
4. Hospital mortality
5. Rate of reintubation
6. Rate of tracheostomy
7. All adverse events (as defined by the study authors).

3.3 Searches

3.3.1 Electronic searches

1.the Cochrane Central Register of Controlled Trials(CENTRAL) ;
2.MEDLINE via Ovid;
3.EMBASE;
See Appendix 1, 2, and 3 for the search strategies.

No restriction in languages.

3.3.2 Other resources

1.the World Health Organization International Clinical Trials Platform Search Portal (ICTRP)
See Appendix 4 for the search strategies.
2.ClinicalTrials.gov
See Appendix 5 for the search strategies.

We will also inspect the references of extracted studies and the international guideline “mechanical ventilation in adult patients with acute respiratory distress syndrome” from American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. (10)

3.4 Strategy for data synthesis

3.4.1 Search strategy

The search strategy described above will be used to obtain the titles and abstracts of studies that may be of relevance to the review. These titles and abstracts will be screened independently by two authors who will discard any studies which are not applicable, although any studies and reviews which might include relevant data or information on trials will be retained initially. We will contact the authors of these studies in order to assist in the screening of these studies if necessary. Two authors will then independently assess the remaining abstracts and, if necessary, their full texts, to determine whether they satisfy the inclusion criteria or not. The two authors will then compare their lists, and any differences in opinion between them will be resolved by discussion and, if this fails, through arbitration by a third author.

3.4.2 Data extraction

Data extraction will then be carried out independently on the studies selected for inclusion by two authors using standard data extraction forms. Again, we will contact authors of these studies if necessary during this process, and any differences in opinion regarding data collection between the authors will be resolved by discussion, or through arbitration by a third author if required. If more than one publication of a given study exists, the reports will be grouped together and the publication with the most complete data used in the analyses. If relevant outcomes have only been published in earlier versions of studies, these data will be used, and any discrepancies between the published versions will be highlighted.

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3.5 Risk of bias assessment

Part A. The impact of PVA on clinical outcomes

Two researchers independently will assess the risk of bias for each study using QUIPS tool (Hyden 2013) (11). We will assess the following domains:

1. Study Participation
2. Study Attrition
3. Prognostic Factor Measurement
4. Outcome Measurement
5. Study Confounding (Age, Severity score, Duration of mechanical ventilation)
6. Statistical Analysis and Reporting

Agreement between the two review researchers with regard to the primary outcomes. Disagreement will be resolved by discussion and if necessary a third review researcher.

Part B. Interventions for improving PVA

Two researchers independently will assess the risk of bias for each randomized control study using risk of bias 2 tool (12).

Two researchers independently will assess the risk of bias for each observational study using ROBINS-I tool (13).

3.6 Assessment of effects of prognostic factor and interventions

For the dichotomous variables of mortality and prevalence of reintubation and tracheostomy, pooled odds ratios (ORs) with 95% CIs are provided.

For the continuous outcomes including duration of mechanical ventilation (expressed in days) and incidence of PVA (expressed in percentage), the standardised mean differences or the mean differences with 95% CIs were calculated, as recommended by the Cochrane Handbook. (14)

Adverse events were narratively summarised because their definition often varies across studies.

3.8Missing values

3.8.1 Discrete variables

For discrete variables, we will analyze all the data following the concept of intention-to-treat (ITT). For continuous variables, we will not perform imputation of missing values, in accordance with the recommendations set out in the Cochrane handbook (14). We will perform meta-analyses using original data.

3.8.2Missing values

We will contact the study authors about missing values.

3.8.3Statistical measurement for missing values

If only standard errors or p-values are reported, the Altman method(15) is used to calculate the standard deviation. If the author is not known, the standard deviation is calculated from the confidence intervals and t-values using the method described in the Cochrane handbook(16) or supplemented by a validated method(17). Alternatively, the standard deviations are complemented by the validated method(17). The validity of these methods will be verified by a sensitivity analysis.

3.9 Assessment of heterogeneity

We will calculate I2 as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%, negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity is identified for an outcome (I2 >50%), we will investigate the underlying reasons and conduct the $\chi 2$ test, with a p value of <0.10 being considered to indicate statistical significance.

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3.10 Assessment of publication bias

We will search trial registers (the World Health Organization International Clinical Trials Platform Search Portal, ClinicalTrials.gov) to identify completed but unpublished trials. If more than 10 studies are included in this review, we will perform a funnel plot analysis and will use Egger's test (a p value of < 0.05 being considered to be statistically significant for a two-sided test) to assess reporting bias.

3.11 Meta-analysis

We will conduct all analyses using the STATA version 16 (StataCorp, College Station, Texas, USA).
We will use the random-effects models for all analyses.

3.12 Subgroup analysis

We will also carry out prespecified subgroup analyses according to the following variables.

1. Causes of admission to ICU: Internal diseases vs. Traumatic diseases
2. Coexisting ARDS: ARDS vs. not ARDS
3. Ventilator mode: Assist control or pressure support ventilation vs. other ventilator mode
4. Timing: Acute phase (within 72 hrs of initiation of mechanical ventilation or as soon as patients were not able to trigger all ventilator breaths) vs Whole period of mechanical ventilation
5. Ways of evaluating PVA: Human vs Software

3.13 Sensitivity analysis

We plan the following prespecified sensitivity analyses for the primary outcomes: exclusion of studies (i) using imputed statistics, (ii) including timing when assessing the PVA is not only acute phase but without acute phase, (iii) including post-operative patients and (iv) with high or moderate risk of bias. Statistical significance was also set at $p<0.05$.

4. Summary of findings

We will create a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. (18)

Part A. The impact of PVA on clinical outcomes

1. Duration of mechanical ventilation
2. ICU mortality
3. Hospital mortality
4. Reintubation
5. Tracheostomy
6. All adverse events (as defined by the study authors)

Part B. Interventions for improving PVA

1. Incidence of PVA
2. Duration of mechanical ventilation
3. ICU mortality
4. Hospital mortality
5. Reintubation
6. Tracheostomy
7. All adverse events (as defined by the study authors)

5. Conflict of Interest

We have no conflict of interest.

6. References

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1. Gilstrap D, MacIntyreN. Patient-ventilator interactions. Implications for clinical management. Am J Respir Crit Care Med 2013;188:1058–1068.
2. Thille AW, Rodriguez P, CabelloB, et al. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006;32:1515–22.
3. de Wit M, Miller KB, GreenDA, et al. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med 2009;37:2740–5.
4. Beitler JR, Sands SA, Loring SH, et al. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria. Intensive Care Med 2016;42:1427–1436.
5. Pohlman MC, McCallister KE, SchweickertWD, et al. Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. Crit Care Med 2008;36:3019 –3023.
6. Blanch L, Villagra A, SalesB, et al. Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 2015;41:633–641.
7. Chanques G, Kress JP, Pohlman A, et al. Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med. 2013;41:2177–2187.
8. Pettenuzzo T, Aoyama H, Englesakis M, et al. Effect of Neurally Adjusted Ventilatory Assist on Patient-Ventilator Interaction in Mechanically Ventilated Adults: A Systematic Review and Meta-Analysis. Crit Care Med 2019;47:e602–609.
9. Kataoka J, Kuriyama A, Norisue Y, et al. Proportional modes versus pressure support ventilation: a systematic review and meta-analysis. Ann Intensive Care 2018;8:123.
10.FanE, Del SorboL, GoligherEC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine.An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253-1263.
11. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med. 2013;158:280.
12. Sterne JAC, SavovićJ, Pageet MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
13. Sterne JAC, Hernán MA, Reeveset BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
14. Higgins JPT, Green S E. *Cochrane Handbook for Systematic Reviews of Interventions Version 6*. updated Ma. The Cochrane Collaboration; 2019. Available at: www.cochrane-handbook.org.
15.Altman DG, Bland JM. Statistics Notes Detecting skewness from summary information Lesson of the Week. 1996;313(November):1996.
16. Higgins JPT, Green S E. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. updated Ma. The Cochrane Collaboration; 2011. Available at: www.cochrane-handbook.org.
17. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006;59:7–10.
18. Foroutan F, Guyatt G, Zuk V, et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks.J Clin Epidemiol. 2020;121:62-70.

ATTACHMENTS

Asynchrony_SR_R2.pdf

DOI

dx.doi.org/10.17504/protocols.io.bsqtndwn

PROTOCOL CITATION

Michihito Kyo, Tatsutoshi Shimatani, Koji Hosokawa, Shunsuke Taito, Yuki Kataoka, Shinichiro Ohshimo, Nobuaki Shime 2021. The impact of patient-ventilator asynchrony in adult mechanically ventilated patients on outcomesA systematic review and meta-analysis. **protocols.io**
https://dx.doi.org/10.17504/protocols.io.bsqtndwn
Version created by Michihito Kyo

Citation: Michihito Kyo, Tatsutoshi Shimatani, Koji Hosokawa, Shunsuke Taito, Yuki Kataoka, Shinichiro Ohshimo, Nobuaki Shime (02/24/2021). The impact of patient-ventilator asynchrony in adult mechanically ventilated patients on outcomesÃ¯Â¼ÂA systematic review and meta-analysis.
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KEYWORDS

mechanical ventilation, intensive care unit, patient ventilator asynchrony, patient ventilator dyssynchrony, acute respiratory distress syndrome, respiratory failure

CREATED

Feb 24, 2021

LAST MODIFIED

Feb 24, 2021

PROTOCOL INTEGER ID

47603

1

Citation: Michihito Kyo, Tatsutoshi Shimatani, Koji Hosokawa, Shunsuke Taito, Yuki Kataoka, Shinichiro Ohshimo, Nobuaki Shime (02/24/2021). The impact of patient-ventilator asynchrony in adult mechanically ventilated patients on outcomesÃ¯Â¼ÂA systematic review and meta-analysis. https://dx.doi.org/10.17504/protocols.io.bsqtndwn