The Effectiveness and Safety of Neurally Adjusted Ventilatory Assist Mechanical Ventilation Compared to Pressure Support Ventilation in Optimizing Patient Ventilator Synchrony in Critically ill Patients: a Systematic Review and Meta-Analysis

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Abstract

Background

Patient ventilator dyssynchrony is a physical characteristic of suboptimal interaction between patient and ventilator. Some primary clinical studies using neurally adjusted ventilatory assist compared to pressure support suggest it improves patient ventilator synchrony and reduces hospital mortality. With conflicting study outcomes, a systematic review of the effectiveness and safety of neutrally adjusted ventilatory assist is warranted.

Objectives

This systematic review aimed to evaluate the effectiveness of neutrally adjusted ventilatory assist (NAVA) compared to pressure support ventilation (PSV) in optimizing patient ventilator synchrony in critically ill adult patients in intensive care unit (ICU).

Methods

Seven databases ; the Cochrane Central Register of Controlled Trials, MEDLINE (PubMed), EMBASE, SCOPUS, ClinicalTrials.gov, Web of Science and CINAHL were searched using the following terms: neurally adjusted ventilatory assist, NAVA, neural trigger, interactive ventilatory support, respiration, artificial, mechanical ventilation, patient ventilator asynchrony, synchrony, asynchrony, dyssynchrony. The last search was conducted in April 2018. This review included studies that evaluated the use of NAVA compared with PSV in adult patients who required invasively mechanical ventilation. Outcomes of interest included the frequency of patient ventilator dyssynchrony (PVD) and mortality from all causes. The methodological

quality of included studies was assessed, and the data were extracted by using standard forms. Standardized mean differences (SMDs) were calculated for continuous data and risk ratios for dichotomous data, both with 95% CIs.

Results

A total of 1,078 articles were identified, for which 210 full text articles were reviewed. In total 17 studies met inclusion criteria. The outcome data were available for approximately 90% of participant (n=398). Neurally adjusted ventilatory assist significantly reduced the AI% by nearly one half of standard deviation; SMD 0.401, 95% CI 0.223 to 0.57, *p value* 0.000 and I^2 0.00% (fixed effect model; two RCTs,128 participants). It was maintained in crossover study group

; SMD 0.304, 95% CI: 0.079 to 0.528, *p* value 0.008 and I^2 75.85% (random effects model, 13 crossover studies, 347 participants). The reduction of the AI% estimated effect size was found to be larger in a sedated group; SMD 0.413, 95% CI: 0.125 to 0.702, *p* value 0.005 and I^2 71.24% than a non-sedated group; SMD 0.225, 95% CI: -0.208 to 0.659, *p* value 0.308 and I^2 86.76% (random effects model, 10 studies, 248 participants). In addition, a higher reduction of AI% effect size was found in a treatment duration longer than an hour group; SMD 0.413, 95% CI:0.044 to 0.782, *p* value 0.028 and I^2 0.00% than a shorter than an hour group; SMD 0.287, 95% CI:0.069 to 0.505, *p* value 0.010 and I^2 77.62% (random effects model, 13 studies,301 participants). Similarly, in a 20- minute and longer PVD event-measurement time group found that NAVA reduced AI% more than in a shorter than 20-minute PVD event -measurement time group; SMD 0.389, 95% CI: 0.109 to 0.668, *p* value 0.006 and I^2 0.00% and SMD 0.267, 95% CI: 0.024 to 0.510, *p* value 0.031 and I^2 82.18%, respectively (random effects model, 13 studies, 301 participants).

Neurally adjusted ventilatory assist was associated with a reduction of the risk of AI>10%; OR 0.688,95% CI:0.514 to 0.921, *p* value 0.012 and I^2 21.93%). It significantly reduced the NeuroSync index; SMD 0.745, 95% CI:0.316 to 1.175, *p* value 0.001 and I^2 0.00% (fixed effect model, two studies, 24 participants). In addition, patients in the NAVA group had a lower patient ventilator asynchrony % than in the PSV group in both two levels of assistance; NAVA-low and NAVA-high (Mean ± SD) 7±2% and 7±2%; PSV-low and PSV-high 18±13% and 23±12%, respectively. Patient ventilated with NAVA had a lower ICU mortality compared to the PSV; OR 0.610, 95%

CI:0.263 to 1.418, *p* value 0.251 and I^2 0.00% (fixed effect model, two RCTs, 153 participants).

Conclusion

Neurally adjusted ventilatory assist is associated with a reduction of PVD frequency compared with PSV. However, effect on lowering the ICU mortality rate is uncertain.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Glossary

ABG	Arterial blood gas
ACV	Assist control ventilation
AI	Asynchrony index
ARF	Acute respiratory failure
BIS	Bispectral index
CNS	Central nervous system
CMV	Control mechanical ventilation
COPD	Chronic obstructive pulmonary disease
Edi	Electrical activity of diaphragm
ETS	Expiratory trigger sensitivity
FiO_2	Partial pressure of oxygen
IEE	Ineffective inspiratory effort during expiration
IMV	Invasive mechanical ventilation
ITI	Ineffective inspiratory trigger index
ITS	Inspiratory trigger sensitivity
CMA	Comprehensive Meta-Analysis (software)
PaO_2	Partial pressure of oxygen in arterial blood
Paw	Airway pressure
PAV	Proportional Assisted Ventilation
PBW	Predicted body weight
PCV	Pressure control ventilation
PEEPe	External positive end expiratory pressure
PEEPi	Intrinsic positive end expiratory pressure
PPS	Proportional Pressure Support™
PSV	Pressure support ventilation
PVI	Patient ventilator interaction
RASS	Richmond Agitation and Sedation Scale
RSS	Ramsay Sedation Scale
TA	Trigger asynchrony
VC	Volume cycle
VCV	Volume control ventilation
VIDD	Ventilator induced diaphragm
VILI	Ventilator induced lung injury
V_T	Tidal Volume
µV	Microvolt

Chapter 1: Introduction

1.1. Introduction

Patient ventilator dyssynchrony (PVD) and suboptimal patient ventilator interaction are common in invasive mechanical ventilation (IMV).[1-4] Patient ventilator dyssynchrony is associated with poor patient outcomes included wasted inspiratory effort,[5] increased work of breathing,[6] prolonged invasive mechanical ventilation [7,8] increased length of stay and higher mortality.[7,9,10] It may also be a cause of adverse patient events including discomfort, dyspnoea, pain, panic and anxiety.[11,12]

Patient ventilator dyssynchrony is a physical characteristic of a suboptimal interaction between patient and ventilator. It can be defined as a mismatch between the patient and ventilator inspiratory and expiratory times or uncoupling of the mechanically delivered breath (ventilator) and neural respiratory effort (patient).[13-15] Patient ventilator dyssynchrony can be identified and categorized into different waveform morphologies. Dyssynchrony characteristics reported in the literature include trigger asynchrony, ineffective effort or ineffective triggering or wasted effort, double triggering, auto triggering,[16] flow asynchrony, premature inspiratory trigger (fast flow delivered), delayed inspiratory trigger (slow flow delivered), cycling off asynchrony, premature expiratory cycling off, delayed expiratory cycling off,[17,18]) and reverse triggering.[19]

There are multiple factors contributing to suboptimal patient ventilator interaction. Of these, mechanical ventilation modes that are used for ventilatory support patient play an important role. Neurally Adjusted Ventilatory Assist (NAVA) is one of many modes that has been shown to optimise patient ventilator synchrony (PVS) when ventilator parameters are adjusted to tailor to patient respiratory demands.[9,10,20-23]. Neurally Adjusted Ventilatory Assist uses an electrical activity diaphragm (Edi) to control the ventilator via a special catheter (Edi Catheter). This mode has been shown to be superior to pressure support ventilation (PSV) in reducing PVD[24-26] and lowering mortality.[9,10]

A preliminary literature search found primary studies have evaluated the efficacy of NAVA compared to standard conventional mechanical ventilation. To date, three homogenous parallel RCT studies evaluated AI% and AI>10%, mortality and other patient important outcomes have been published.[9,10,27] This evidence suggests there is sufficient data to evaluate how effective NAVA is in optimizing patient ventilator synchrony, and what effect dyssynchrony has on patient outcomes when compared to standard conventional IMV (conventional mechanical ventilation is defined as PSV mode (see Appendix I: systematic review protocol)).

This systematic review was conducted using The Joanna Briggs Institute (JBI) methodology for guidance.[28-32] The guidance of JBI for conducting a systematic review of effectiveness research involves a rigorous analysis and synthesis of available evidence from a systematic and comprehensive search of literature, then summarizes the evidence, providing resources to health care professionals.[33] This provides evidence-based information to policy makers and clinicians, and therefore improves clinical practice and health outcomes. The aim of this systematic review is to provide and expand knowledge in patient ventilator interaction, to inform clinicians in managing dyssynchrony in IMV patients and to meet the requirements of a Master of Clinical Science Degree.

1.2. Structure of dissertation

This dissertation is organised into 5 chapters. It includes:

Chapter 1: Introduction: the first chapter describes the context of the systematic review including the review objective and questions, patient ventilator interaction, patient ventilator dyssynchrony classification, calculation of PVD frequency, and factors contributing to PVD and PVD associated patient outcomes. Current literature in the field is described, and evidence-based practice and evidence-based healthcare in patient ventilator management.

Chapter 2: Background: The second chapter outlines indications for invasive mechanical ventilation, PSV and NAVA and measurement of treatment effects.

Chapter 3: Methods: The third chapter describes the methodological process for this

systematic review contained within this thesis. It outlines the inclusion criteria for the systematic review. These include type of participants, interventions, comparators, outcomes and studies. This chapter also describes the systematic review methodology used for the search strategy: search method, search finding outcomes and assessment of methodological quality: critical appraisal step, data extraction and data synthesis.

Chapter 4: Results: The fourth chapter presents the description of the included studies, search results, methodological quality results and overview of included studies. It outlines outcomes of interest and summary of review findings. The findings of the systematic review outcomes are outlined in the meta-analysis report of AI%, AI>10%, NeuroSync index, the narrative summary of patient ventilator asynchrony percentage (PVA%) and intensive care (ICU) mortality.

Chapter 5: Discussion: The final chapter discusses the main finding outcomes from extracted data within the included studies in the context of existing literature to answer the review questions and identifies the limitations of the systematic review process. It describes implications for practice and research.

1.3. Review objective/questions

The objective of this systematic review was to systematically identify, appraise and synthesise the best available evidence on the safety and effectiveness of IMV in optimizing patient ventilator interaction by using NAVA compared with PSV in critically adult patients in ICUs. To evaluate the safety of NAVA is by analysing whether it causes higher PVD event and mortality rate. These IMV associated events are considered preventable. According to World Health Organization patient safety is defined as “the absence of preventable harm to a patient during the process of healthcare”.[34] The specific questions this review sought to address were:

> Does NAVA influence patient ventilator synchrony measured by using AI%, NeuroSync index and PVA% compared to PSV among critically ill adult patients on IMV support in an intensive care environment?

What is the evidence of safety, related to use of NAVA, compared with PSV when used in critically ill adult patients in an intensive care environment?

1.4. Patient ventilator interaction

Mechanical ventilation is a respiratory function support used in the presence of acute respiratory failure when patient ventilatory capabilities are unable to adequately meet physical demands. Precipitating causes of respiratory inadequacy include acute respiratory failure, coma, chronic obstructive pulmonary disease (COPD) exacerbation, and neuromuscular diseases.[35-37] The goals of mechanical ventilation support are to optimize gas exchange, improve patient comfort and reduce work of breathing.[38] Furthermore, in spontaneous breathing with assisted IMV (defined as a patient breathing spontaneously to trigger and cycle off the ventilator, and the breath is assisted by the ventilator using either pressure control or volume control), the patient's work of breathing should be supported adequately and synchronously with the activity of the patient's intrinsic respiratory rhythm.[15,39]

Patient ventilator interaction is an interplay between two complex systems, the patient's respiratory system that is driven by individual patient metabolic demand and a mechanical ventilator.[40] With advanced microprocessor technology most ventilators are adjusted either by operators, or by artificial intelligence systems embedded into ventilators to optimize patient ventilator interaction.[41-43] In the spontaneously breathing mechanically ventilated patient, the ventilator should deliver ventilatory assistance perfectly matched to the patient's respiratory effort and sufficient unloading of the respiratory muscle work, and in responding to this the patient would breath synchronously with the ventilator.[44] Important objectives of partial ventilatory assist are to respond efficiently to patient respiratory demands,[45] to sufficiently unload respiratory muscle work,[46,47] to avoid ventilator induced lung injury (VILI),[48] and to prevent ventilator induced diaphragm dysfunction (VIDD).[49-51]

Optimized patient ventilator interaction has been reported to improve important patient outcomes. The percentage of successful weaning was found to be higher in a group of patients who did not have patient ventilator triggered asynchrony (TA), and those who had a better patient ventilator interaction had shorter durations of IMV and lower tracheostomy and mortality rates.[8,45] Suboptimal patient-ventilator interaction has been described as patient ventilator asynchrony (PVA),[45] ineffective expiratory effort (IEE),[7,52] PVD[53] and TA.[8] In this review, the term dyssynchrony "*dys a prefix which* means bad, difficult; GREEK" is used to define all terms that mean failure of synchrony between the patient and ventilator.[54]

1.5. Patient ventilator dyssynchrony classification

Patient ventilator dyssynchrony can be identified and categorized by waveform morphology. It includes trigger asynchrony, ineffective effort or ineffective triggering, double triggering, auto triggering, flow asynchrony, premature inspiratory trigger (fast flow delivered), delayed inspiratory trigger (slow flow delivered), cycling off asynchrony, premature expiratory cycling off, delayed expiratory cycling off, and reverse triggering.[38,45,55,56, 57-62]

Studies have reported eight different types of patient ventilator interaction. The main dyssynchrony characteristics are type (i) to (iii). These eight patterns of dyssynchrony are defined as follows:

(i) Ineffective triggering (IT) is also known as wasted efforts, and defined as one positive Edi deflection with or without airway pressure drops and not followed by an assisted breath, [45,16] or a deflection in airway pressure (Paw) corresponding to a decrease in expiratory flow not followed by either a ventilator cycle or an increase in inspiratory flow during a ventilator assisted breath.[63] This is a type of suboptimal patient ventilator interaction when the ventilator fails to deliver inspiratory breath after the patient makes a neural inspiratory effort.

(ii) Double triggering (DT) is defined as two assisted breaths delivered during a single positive Edi deflection or airway pressure drop,[16,45] or characterized by the presence of two ventilator insufflations separated by a brief (i.e. less than

half of the average inspiratory time) expiratory time, in which only the first cycle was properly triggered by the patient.[63]

(iii) Auto-triggering (AT) is defined as a mechanically delivered breath without an associated positive Edi deflection and without airway pressure drop,[16] or a ventilator cycle without a preceding Paw deflection.[63]

(iv) Triggering delay/ inspiratory trigger delay is defined as the time difference between the onset of inspiratory effort and the beginning of ventilator pressurization.[23,64]

(v) Cycling delay is defined as the time difference between the end of neural inspiration and the ventilator inspiratory flow.[65]

(vi) Premature cycling is defined as an assisted breath with expiration starting before the end of patient's effort as assessed by Edi (i.e. before Edi peak or right after it and/or with biphasic expiratory flow waveform).[16]

(vii) Short cycle is defined as a mechanical inspiratory time (Ti_{mech}) less than one-half of the mean $Ti_{mech.}$[64]

(viii) Prolonged cycle is defined as a mechanical inspiratory time greater than twice the mean $Ti_{mech.}$[64]

The goals of patient ventilator interaction are to optimize PVS and to minimize PVD by setting and adjusting mechanical ventilatory assist parameters to effectively match patient intrinsic respiratory rhythm and demands simultaneously. In the partial mechanical ventilatory assist mode the breaths are initiated by the patient inspiratory effort. An interaction between patient and ventilator is sensed by the ventilator, which is called a trigger. There are two parts of the trigger that need to be set up by an operator in most modern ventilators. They are an inspiratory trigger (to initiate the inspiratory breath) and expiratory trigger (to end inspiratory breath or to initiate expiratory breath). In the pneumatic trigger system, the patient triggers the ventilator by generating the airflow or pressure. When the pressure or air flow reaches the trigger-threshold setting in the ventilator, which is called inspiratory trigger sensitivity (ITS), the ventilator delivers the breath. Breath delivery is achieved by targeting either a flow (flow targeted breath) or a pressure (pressure targeted breath). Similarly, when the flow or pressure is terminated, the expiratory trigger sensitivity (ETS) is reached and the ventilator ceases assisting breaths. However, in the neural trigger system in

NAVA, the inspiratory and expiratory breaths are triggered to initiate and terminate the assisting breaths by the patient's neural inspiratory effort, which is measured from the Edi catheter. The neural inspiratory and expiratory trigger thresholds need to be set and adjusted to optimize PVS. The trigger threshold sensitivity is adjusted by the Edi value. Cycling off occurs when termination of inspiration and is achieved when a pre-set target (pressure or volume or time) has been delivered. In PSV, breath is terminated when the flow reaches a pre-set proportion of the peak flow, which is called the cycling off sensitivity/ETS. In NAVA, the ventilator cycles off when the Edi value drops to a pre-set ETS value.[47,66] Pressure support and NAVA are pressure targeted and are always patient triggered. The speed at which the targeted pressure is reached is called the rise time.[67] Various methods have been developed to capture a dyssynchrony event and to calculate it's frequency.

Figure 1 shows graphic waveforms illustrating the respiratory breathing cycle identified by pressure, flow and Edi waveforms, while figure 2 shows an ideal patient ventilator interaction (perfect patient ventilator synchrony).

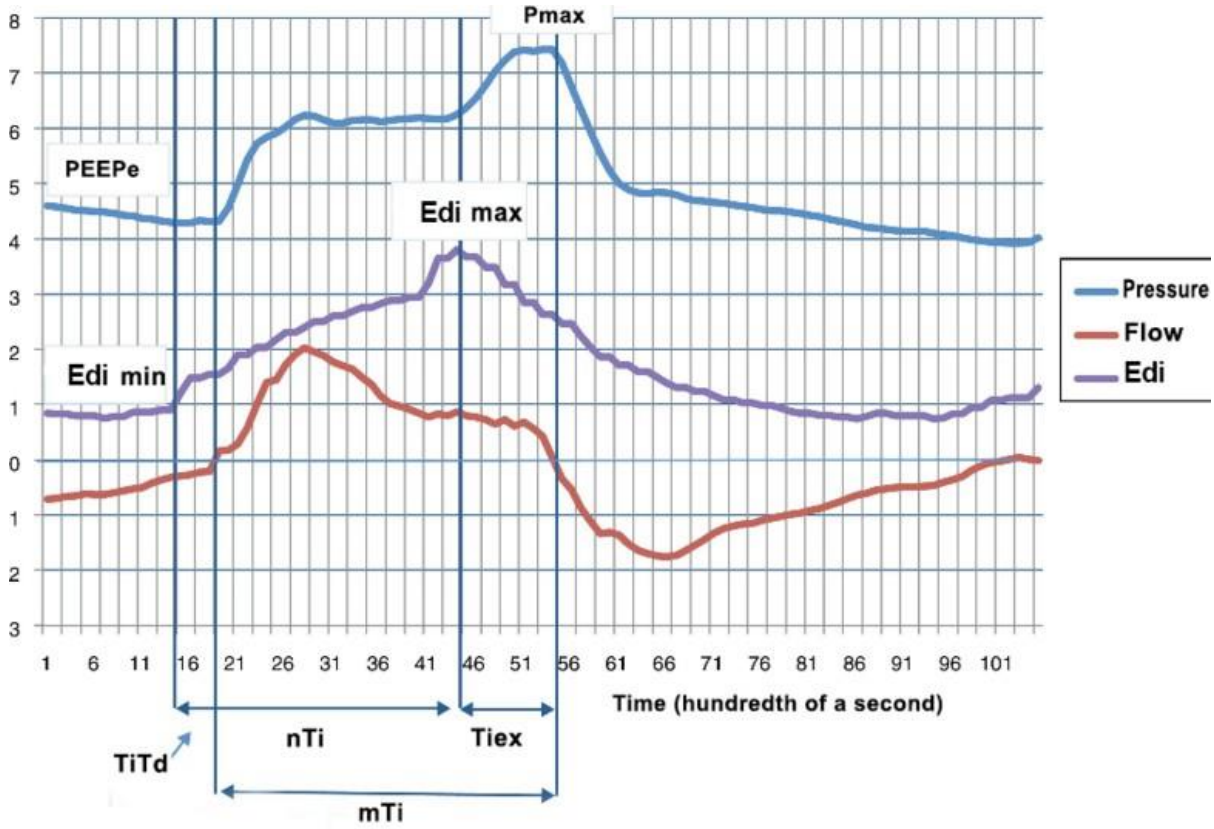


Figure 1: Graphic waveforms of pressure, flow and Edi are used for visual inspection to detect patient ventilator dyssynchrony (adapted from Garcia-Munoz et al 2016).[68]

Edi-min: Electrical activity minimum value; Edi-max: Electrical activity maximum value / peak value; nTi: neural inspiratory time; mTi: mechanical (ventilator) inspiratory time; PEEPe: external positive end expiratory pressure); Pmax: inspiratory airway pressure maximum / peak; Pressure (airway pressure- cmH_2O); Tiex: inspiratory time in excess; TiTd: inspiratory trigger time delay

1.6. Calculation of patient ventilator dyssynchrony frequency

Patient ventilator dyssynchrony detection in this review is based on an objectively measured time mismatch between either airway flow or airway pressure (Paw) graphic waveforms to oesophageal pressure (Pes) waveform or Edi waveform. To calculate incidence of patient ventilator dyssynchrony, two main calculation methods were included, which are an asynchrony index [45] and NeuroSync index.[25] The primary investigators of many synchrony related clinical trial studies frequently used the formula of Thille et al.[45] In this formula the AI is calculated as follows:

AI (expressed as percentage) = number of dyssynchrony events ÷ total respiratory rate (ventilator cycles + wasted effort) x 100.

The total dyssynchrony events are measured in minutes or total duration of recording time during an intervention study period or during a control study period, or as reported by the investigator of the study, then it is reported as a percentage of total asynchrony events.

The NeuroSync index is a percentage and detected by comparing the Edi and Paw timing dissociation. It is calculated by identifying the trigger error (P_{ON}-Edi_{ON}) and the cycle off error (P_{OFF}-Edi_{OFF}) divided by the neural inspiratory detection period and number of neural expiratory detection periods X 100. An automated computer algorithm is used to capture and report these timing dissociations and the NeuroSync index is calculated by averaging the error for all breaths per minute per mode. A

complete dissociation between Edi and Paw, including wasted effort, auto triggering and double triggering are defined as a 100% error and asynchronous breaths. Breaths with absolute error of less than 33% are defined as synchronous, whereas breaths with absolute error more than 33% are defined as dyssynchronous breaths.[25]

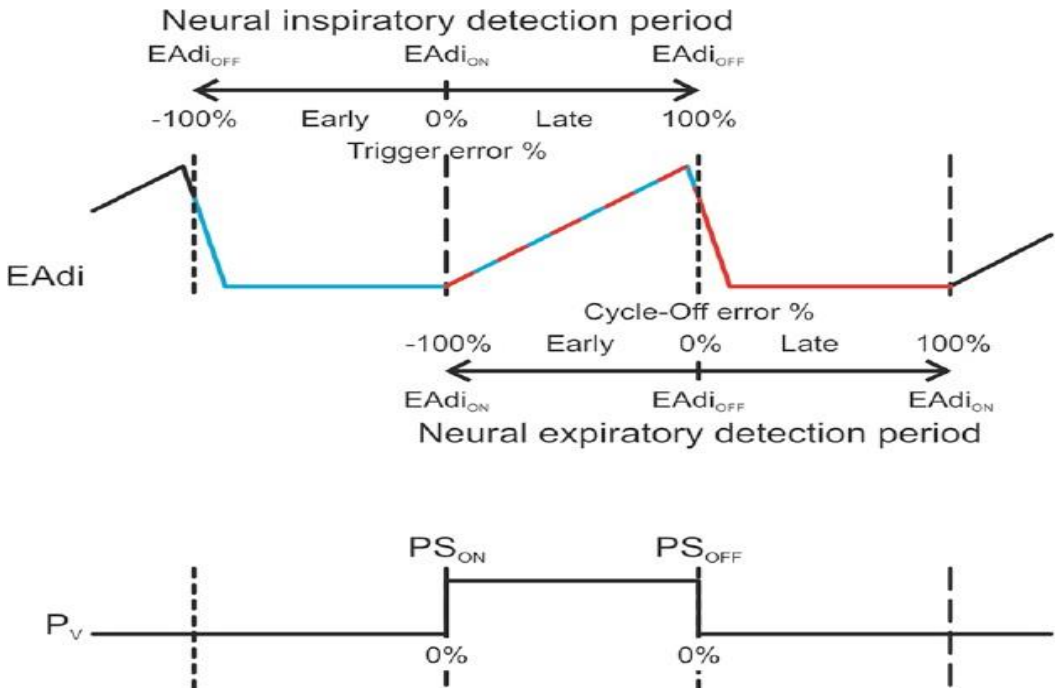


Figure 2: Graphic of patient ventilator perfect synchrony (adapted from Sinderby et al)[69]

EAdi (Edi): electrical activity of diaphragm; Pv: ventilator pressure; PS: pressure support

1.7. Factors contributing to patient ventilator dyssynchrony

Patient ventilator dyssynchrony is highly prevalent. Seventy six percent of 36 patients in one study who had a variety of precipitating causes of acute respiratory failure were found to have ineffective effort. Their IMV days ranged from 15 to 50 days, and 55.5% of these patients had COPD.[11] In other studies, the dyssynchrony event rate was reported as high as 87.9% in COPD patients in the respiratory care centre who were ventilated for more than 21 days.[27] Moreover, in medical critical care patients'

ineffective triggering was found in 85% of 20 IMV patients, and ineffective trigger events accounted for 88% of all dyssynchrony events.[70] Patient ventilator dyssynchrony events are contributed to by numerous factors including patients,[71] ventilator modes,[23] operators,[63] level of assistance[2,11,46] and measurement factors.[27,72] Patient related factors include patient demographic characteristics and comorbidities.[16]

1.7.1. Patient factors

Chao et al investigated 174 patients with prolonged IMV using a flow controlled, volume cycling mode. It was found that 10.9% of them had TA on initial assessment. Trigger asynchrony events were identified by detecting uncoupling of the patient's accessory respiratory muscle efforts and onset of ventilator breaths. Of this group, patients were significantly older, diagnosed with COPD, had a higher mean partial pressure of carbon dioxide ($PaCO_2$) and a lower mean peak airway pressure compared to the group that had no TA.[8] Similarly, Nava et al found that ineffective effort was higher in COPD patients than ARDS and post-surgical complication patients while ventilated with PSV.[73]

In a study to evaluate AI% in 10 ARDS patients with extremely low respiratory compliance undergoing extra corporeal oxygenation (ECMO), Mauri et al found that patients' mean AI% ,measured by using Edi compared to flow tracing, was very high in all three study arms: PSV with ETS30%(103 ± 61), PSV with ETS1%(74 ± 43) and NAVA (20 ± 13).[16] Duration of IMV also plays an important part in increased asynchrony incidence. In addition, sedative agents that effect conscious stages were found to induce poor patient ventilator interaction in PSV with flow trigger, in the study by Vaschetto et al. Patients under deep sedation had the highest ineffective triggering index (ITI) of 21.8% in patients who were ventilated with PSV, but no incidences of ITI were found in the NAVA group.[26] Likewise, de Wit et al found deeper levels of sedation increased ITI in medical patients ventilated with synchronized intermittent mandatory ventilation (SIMV) mode with pressure support, PSV mode and PCV mode. The ineffective triggering index was 2% in awake patients compared to 11% in non-awake patients and as high as 15% in heavily sedated patients.[70]

1.7.2. Ventilator factors

Ventilator factors include manufacturer specifications. A study of modern ventilators used in the ICU reported that inspiratory delays differ significantly among 13 different ventilators, and delay times range from 75–149 milliseconds (ms) (p=0.03).[74] Similar outcomes were found in testing of 13 modern ICU ventilators; four were turbine-based and nine were conventional servo-valve compressed-gas ventilators with a validated two-chamber Michigan test lung in PSV mode. Trigger delays in ms were found to have a significant difference between all ventilators, 58 ms range 42-88ms (p=0.0001).[75] Other ventilator factors that can cause PVD include non-invasive positive pressure ventilation[76-78] and heated humidification circuits.[13,79]

1.7.3. Clinician knowledge and skill factors

Operator related factors may include knowledge and skills of clinicians and investigators who pre-set and adjust the ventilator and detection settings for PVD. These factors may contribute to suboptimal ventilator settings.[45,61,80,81] Adjusting the ventilator setting, i.e. tidal volume target, levels of assistance/ pressure support,[5,63,65] ITS,[13] external positive end expiratory pressure (PEEPe),[6] and ETS,[16] can also optimize PVS. Appropriate recognition, analysis and management of PVD also requires the knowledge, skills and appropriate tools to assess ventilator graphic waveforms. In a study to assess the ability of 10 expert and 10 non-expert ICU physicians in identifying patient ventilator dyssynchrony by using visual inspection method, three types of asynchrony (IT, DT and AT) from 43 reports of patients' ventilator interaction graphic waveform. The flow, Paw and Edi ventilator graphic traces, were used. These patients were ventilated in PSV. It was found that specificity from breath by breath analysis by experts was significantly higher than non-experts at 28%, (95% CI: 19-36) compared to 16% (95% CI: 9-23); p =0.03 respectively. In contrast, the non-expert performance specificity was higher than expert at 93% (95% CI: 85-97) and 88% (95% CI: 83-93) p=0.10 respectively. The positive predictive value of experts was lower compared to non- expert at 31% (95% CI: 24-42) and 32% (95% CI: 28-41) respectively, but not statistically significant with a p value of 0.77. However, the negative predictive value was slightly higher at 87% (95% CI: 85-88) compared to

non- expert at 86% (84-86) but was not a statistically significant difference with a *p* value of 0.10. [80] In contrast, one study found the number of dyssynchrony events visually inspected by two observers was highly correlated.[45]

1.7.4. Measurement factors

Measurement modalities may contribute to detecting a prevalence of PVD, modalities of measurement including using graphic waveforms i.e. Paw, flow, Edi and Pes, and using different time durations i.e. intermittent manual inspection and automated real-time computerized measurements. [7,10,45,46,52,82-87] Kuo et al investigated patient ventilator asynchrony incidence rates before and after using an Edi catheter, Paw vs flow tracing compared to Paw vs Edi tracing. These were 60.6% vs 87.9%, $p<0.001$. Similarly, the numbers of dyssynchrony events (AI %) found to increase from 7.4%±8.5% vs 13.2±13.5 %,(mean ± SD) after the Edi catheter was used.[27] In addition, Mauri et al reported AI_{Edi}% was higher than $AI_{(Paw-flow)}$%, (data from personal communication, see Appendix IV), when used to identify PVD events in a crossover study of ARDS patients in NAVA group 20±3 and 16±9, and in PSV1(1% ETS) 74±43 to 44±16 (mean ± SD).[16]

In a study to validate mathematical algorithms, Better Care, it automatically detects ineffective respiratory efforts during expiration (IEE). The Better Care was used to detect IEE by evaluating flow and Edi traces. The Better Care identified IEE by using Edi tracing found to have a better specificity and positive predictive value but lower sensitivity (65.2% sensitivity, 99.3% specificity, 90.8% positive predictive value, 96.5% negative predictive value, and 73.9% Kappa index (95% CI:71.3%- 76.3%), compared to flow tracing (91.5% sensitivity, 91.7% specificity, 80.3% positive predictive value, 96.7% negative predictive value and 79.7% Kappa index (95% CI:75.6% to 83.8%).[52]

The prevalence of PVD also varies with the time of day. The prevalence of AI is found to be highest between 6 am to 12 pm and the lowest from 12 am to 6 am, with median and interquartile range (IQR) of 2.14% (0.69-5.51) and 1.69 (0.47-4.78), respectively.[7] Patient ventilator dyssynchrony events are globally recognized as an important

surrogate outcome when IMV is instituted to support patient's respiratory function and demands. A high number of PVD events using AI>10% has been studied and found to associated with higher patient mortality and other negative patient outcomes.[9,27]

1.7.5. Patient ventilator dyssynchrony associated patient outcomes

Invasive mechanical ventilation is a life support intervention that is commonly used in ICU. The use of IMV with PSV and other standard conventional mechanical ventilation modes in critical ill patients is increasing; a prospective international study in 349 ICUs from 23 countries identified that 25% of patient admitted to ICU were mechanically ventilated for more than 12 hours.[88] However, a one day point prevalence of two studies, one in 55 ICUs in Australia and New Zealand, and another one in 83 ICUs in Poland, found that the numbers of patients mechanically ventilated is more than double that of an international study, at 58% and 73% respectively.[35,89] The incidence of dyssynchrony associated with the use of IMV also appeared to increase when an Edi catheter was used to identify PVD events.[27]

Patient ventilator dyssynchrony is associated with suboptimal patient outcomes including longer duration of IMV, longer ICU and hospital length of stay, and less likely to be discharged home in a group of patients who had ITI>10%. [56] Similarly, a group of AI>10% patients had a longer duration of IMV, higher rate of tracheostomy,[45] higher ICU and hospital mortality.[7] Moreover, three RCT parallel studies reported the AI% in patients in a NAVA group were significantly lower than in a PSV group, mortality was also lower than in the PSV group.[9,10,27] In addition, PVD may also be a cause of patient adverse events including discomfort, dyspnoea, pain, panic and anxiety.[11,12]

There have been reports of important patient outcomes associated with PVD with different ventilator parameter settings, modes, demographic characteristics and healthcare settings. A prospective cohort study of a group of 174 tracheostomized patients who were ventilated in a volume cycled (VC) mode with pressure trigger in a

regional weaning centre, reported that only three of 19 (16%) patients with inspiratory trigger asynchrony were successfully weaned from IMV after 70, 72 and 108 days. In contrast, 57% of patients who had undetected inspiratory trigger asynchrony were successfully weaned with a median IQR of 33 days (3-182).[8]

Patients with AI >10% had similar intubation and tracheostomy rates, a trend toward a longer duration of IMV, and their ICU and hospital mortality rates were significantly higher than in patients who had AI <10%.[7] In contrast, the mortality rate of 16 patients who had an ineffective trigger index (ITI) ≥10% was found to be not statistically different to a group of patients who had an ITI <10% among a cohort of 60 patients. However, ICU and hospital length of stay were reported to be longer when ITI was >10%.[56]

Similarly, an observational study was conducted to investigate PVD in 62 medical intensive care patients requiring IMV for more than 24 hours with a Ramsey Sedation Scale (RSS) median and IQR of 3 (2–5). Eighty-two percent of patients were ventilated on PSV mode and 18% were on assist-control ventilation (ACV). The investigators found that 24% of patients had an AI >10% and a median and IQR of 26% (18-31), respectively. Patients with AI >10% were found to have a longer duration of mechanical ventilation and were likely to be on IMV for more than seven days and be tracheostomized.[45]

In a study comparing NAVA to PSV, 25 patients who were ventilated with control mechanical ventilation (CMV) for at least 72 hours were randomly to be ventilated for 48 hours with NAVA (13 patients) or PSV (12 patients). Patient ventilator interactions were visually detected offline from the pressure airway opening (P_{AO}), flow and Edi digital records of the last 10 minutes of each 4-hour period (total 120 minutes). The AI was found to be higher in patients ventilated with PSV, who had a median and IQR of 9.48 (6.38 – 21.73), than in patients ventilated with NAVA, having a median and IQR of 5.39 (3.78 – 8.36), p=0.04. Moreover, mortality was higher in the PSV group (25%)

compared to the NAVA group (23%). In contrast, the IMV day was similar (mean ± SD) 5.1 ±1.3 versus 5.1 ± 1.7 days, respectively.[10]

There have been conflicting patient dyssynchrony-related outcomes reported in IMV studies. This systemic review aims to evaluate the effectiveness of PSV compared to NAVA in optimizing synchrony for better patient outcomes.

1.8. Current literature on Neurally Adjusted Ventilatory Assist

Since spontaneous breathing with assisted, pressure trigger IMV was introduced into clinical practice decades ago.[90] The different modalities of trigger and sensing in the mechanical ventilator have been further developed to include flow triggers and flow shape/waveform triggers.[56,91,92] With progressive advances in microprocessor and computer technology, subjective identification of patient ventilator interactions by detecting airway pressure, flow, volume and oesophageal pressure waveforms became feasible.[73,93-96] The latest trigger modality, a neural trigger (using Edi), was invented and patent in 1995.[97] It is being used in some clinical settings.[1,98-103] NAVA is a mode that uses an Edi catheter to capture, filter and amplify the electrical activity of the diaphragm, then the modified Edi is used to trigger and cycle off mechanical ventilation. In addition, the Edi waveform also has been used to monitor patient ventilator interaction and to identify PVD.[63,104,105] A growing body of clinical research concludes that NAVA is associated with optimal patient ventilator interaction by minimizing PVD when compared to PSV. It lowers AI,[1,9,20,59,65,106-108] has less timing inspiratory trigger [109] and cycling off responses,[1,10,64,65,109] and a lower NeuroSync index,[25,110]These PVD events are identified by either using a visual inspection of the respiratory graphic display waveforms compared between Paw and flow to Pes and/or to Edi, and using an automated computer analysis software.

A search of the literature uncovered one review that analysed studies that used NAVA in children who were ventilatory supported with invasive and non-invasive NAVA.[111]

However, there were no systematic reviews identified comparing the effectiveness and safety of NAVA with PSV in adult patients. Given the clinical impact of PVD, numerous studies have individually reported strategies to optimize PVD by managing patient ventilator interaction. This includes reduced discomfort, shorter length of stay, prevention of ventilator induced diaphragm dysfunction (VIDD), avoiding ventilator induced lung injury (VILI) and lowering mortality in critically ill patients and in prolonged IMV patients by using different modes of IMV, such as PSV, NAVA, PCV and ACV. Therefore, it is timely to compare the effectiveness of clinical application of NAVA to PSV mode in a systematic review, with the aim to assess the methodological quality of included studies and quantitively synthesize these results. There are similarities and differences to the ventilator modes that clinicians must be aware of to ascertain which method is most applicable based on the best quality of rigorous and transparent syntheses of available scientific evidence to support the practice.

The protocol for the research conducted in this thesis was published and available online.[112] However, this systematic review report presents a new revised systematic review protocol It was modified for appropriateness so as to meet the requirement of the Master of Clinical Science degree. The revised systematic review protocol is presented in Appendix I. This systematic review reports a statistical synthesis of data (meta-analysis) of finding outcomes including AI%, AI>10%, NeuroSync index and mortality, and in a narrative writing style of PVA%.

1.8.1. Evidence based practice and evidence-based healthcare in patient ventilator management

With evidence-based medicine, evidence-based healthcare and evidence-based practice becoming prominent, nurses and other clinicians are expected to use research evidence to support their decision making. Since the first *Evidence-Based Guidelines for Weaning and Discontinuing Ventilatory Support* A Collective Task Force Facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine'* was published in 2001, it has been cited more than 1,199 times to date.[113] This evidence suggests that patient ventilator interaction and management in critically ill

IMV patients are crucial and imperative in ICU practice. Moreover, the Cochrane collaboration continues to update a review of weaning adult patients in ICU setting, using a weaning protocol compared to not using weaning protocol/ usual care which was first published in 2014.[114] The outcomes were that a total geometric mean duration of mechanical ventilation on average was reduced by 26% and that there was no difference in ICU and hospital mortality, using data synthesised from 14 studies. However, the authors did not report the weaning protocols using ventilator setting parameters to optimize patient ventilator interaction by optimizing PVS.[114]

In searching for the best intervention for IMV patients in ICU who developed ARDS, *The ARDS Network* was established in 1994. The network has a goal to efficiently test promising agents, devices, or management strategies to improve the care of patients with ARDS. It has conducted 10 RCTs and one observational study and enrolled 5,527 patients into the studies to date. The network provided validated tools for clinicians' practice with ARDS patient groups. Its Clinical Network Mechanical Ventilation Protocol provided ventilator parameter settings, and patient goals (oxygenation, PH and plateau pressure goal) have been published. [115] Notably, optimization patient ventilator interaction by using PVS was not in the goals.

A ventilator synchrony study using Edi graphic measurement was published in 2007,[116] Since then patient ventilator interaction (synchrony, asynchrony and dyssynchrony) has been studied extensively. Investigators have been using the PVD event index (AI%, IEE and NeuroSync index) as a surrogate patient outcome. However, to this authors' knowledge the guideline and protocol for optimizing patient ventilator interaction/ synchrony has never been established. An overview of data from 17 included studies in this systematic review found investigators used/ adjusted different ventilator parameters to optimize settings for a better synchrony based on investigators' and ICU physicians' knowledge and skill. To provide the best available evidence at the point of care, in the evidence synthesis of optimizing patient ventilator interaction by using the latest technology (Edi catheter/ NAVA) compared to PSV, the JBI systematic review process is used. This process follows five series of the

systematic review, step by step. In the systematic review there is an overview, [33] developing the review question and inclusion criteria,[31] constructing a search strategy and searching for evidence, [28] study selection and critical appraisal,[30] and data extraction and synthesis.[29]

Chapter 2: Background

This chapter discusses indications for IMV in adult patients, mechanical settings of PSV, NAVA and measurement of treatment effects.

2.1. Indications for invasive mechanical ventilation

Indication for IMV support are based on the patients' clinical presentation and past medical history; biological parameters and pulmonary function evaluation are also required.[118] Studies report that the most common indication to institute IMV is acute respiratory failure (ARF). A point prevalence study has found that 66% of patients who required intubation had ARF while other studies have found acute respiratory failure can be as high as 88.9% (a study of 55 ICUs in Australia and New Zealand). [117, 89] Some studies also report that clinicians use risk of developing respiratory failure and clinical signs of respiratory distress as reasons to provide IMV support.[118-120]

2.2. Pressure support ventilation

Pressure support ventilation is one of the most frequently used partial ventilatory support modes, as indicated by an international survey on mechanical ventilation across 361 ICUs in 20 countries published in 2002. Pressure support ventilation was used as a weaning process in almost 21% of patients.[121]

Pressure support is a partial ventilatory assist mode, which provides targeted pressure. The breath is patient triggered and the ventilator delivers a constant preset pressure. It allows the patient to initiate and terminate the breathing cycle. When the ventilator ITS threshold is reached, the preset targeted pressure support is provided breath-by-breath synchronously with patient respiratory effort. Inspiratory trigger sensitivity can be set as either a pressure trigger or a flow trigger. In addition, pressure support is maintained until the machine determines the end of expiration. The expiratory trigger sensitivity is based on declining inspiratory flow. As inspiratory flow falls below a cycling off threshold value (ETS level), such as between 2 to 6 L/min or 12 % or 25% of peak inspiratory flow, depending on the manufacturer's algorithm, the ventilator

cycles to the expiratory phase releasing the pressure support and opening its expiratory port.[122-124]

Pressure support can be divided into three phases (i) recognition of the beginning of inspiration, (ii) pressurization provided, and (iii) recognition of the end of expiration.[122] The operator sets a level of pressure (targeted pressure) but not a flow setting, then when the patient initiates the spontaneous effort to reach the ITS threshold, the assist-targeted pressure is provided. The respiratory parameters that can be altered by the patient are respiratory frequency, inspiratory time, and tidal volume.[125] Adjusting a preset pressure support by increased pressure level in PSV mode has been found to increase ineffective effort.[46]

Pressure support ventilation was found to relieve discomfort from IMV when compared with volume controlled continuous mandatory ventilation (VC-CMV). The mean comfort score of PSV was significantly higher than VC-CMV, which was 83 ± 11, 95% CI: 76.9-89.6 and 70 ±18 95% CI: 59.4-79.9, respectively.[126] A systematic review compared PSV with T-tube during a spontaneous breathing trial (SBT) and found that PSV had a significantly higher rate of success in SBT (RR 1.09,95% CI:1.02 to 1.17, p=0.009), risk difference (RD) 0.07,95% CI:0.02 to 0.12, p=0.009, I^2=0.000%, a pooled estimated size from four studies with moderate quality of evidence. Despite this positive outcomes in higher comfort score and rate of success in SBT, PSV demonstrated no difference in weaning success, ICU mortality, reintubation rate, ICU and long-term weaning unit length of stay, and adverse event (pneumonia).[127] In addition, a mean cost of care in PSV was higher compared with proportional assist ventilation (PAV™),[128] and PSV was less cost effective when compared to NAVA.[128]

2.3. Neurally Adjusted Ventilatory Assist (NAVA)

Neurally Adjusted Ventilatory Assist is a relatively new mode of mechanical ventilation.[129] The unique feature of NAVA is it uses the diaphragmatic electrical activity signal to control the ventilator. The electrical activity of the diaphragm is collected from electrodes placed on an orogastric catheter or nasogastric catheter.

During NAVA, positive pressure is applied to the airway opening in direct proportion to the Edi amplitude, so a pre-defined pressure or volume is not required. The catheter is placed in the esophagus at the level of gastro-esophageal junction such that the direction of the electrode array is perpendicular to the diaphragmatic fibers, illustrated in *Figure 3*. Neurally Adjusted Ventilatory Assist does not require measurement of respiratory system mechanics in sensing and responding to the patient respiratory demand.[130] In Figure 4, a diagram of an ideal mechanical ventilation to optimize patient ventilator interaction is presented.

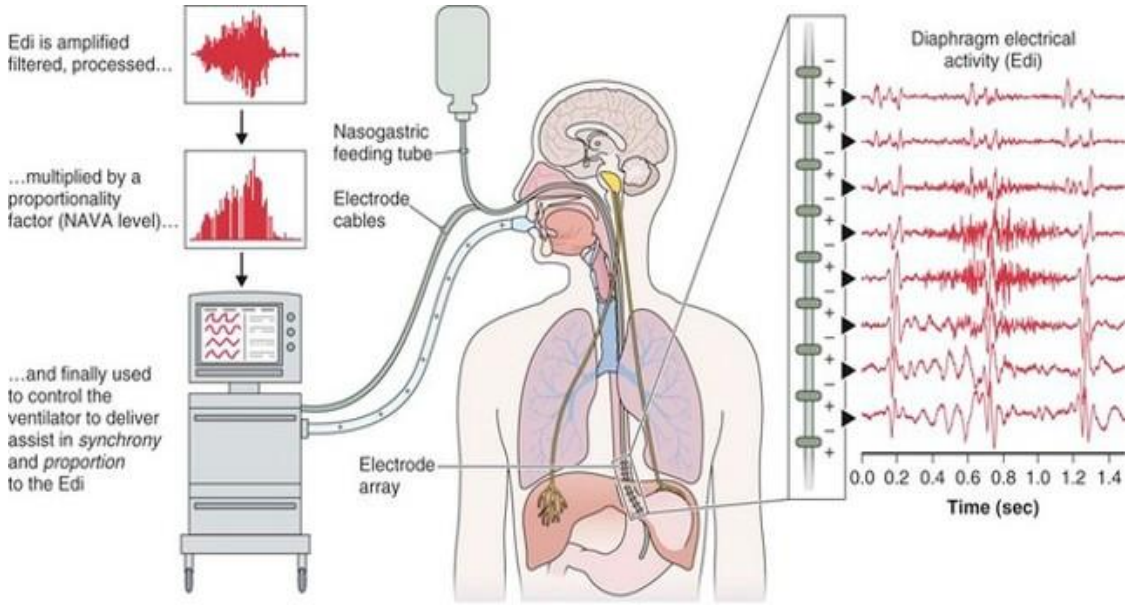


Figure 3: Demographics of diaphragmatic activity in Neurally Adjusted Ventilatory Assist

The electrical activity of the diaphragm (Edi) is derived by use of an array of electrodes mounted on a nasogastric tube, then signals from each electrode pair on the array are differentially amplified, filtered, and multiplied by a proportionality factor (NAVA level) before the signal is used to control the pressure generated by the ventilator Hence, with NAVA, the pressure delivered to the patient is synchronous and (virtually) instantaneously proportional to the patient's Edi (adapted from Sinderby et al 1999 and Brander & Slutsky2015). [100,131]

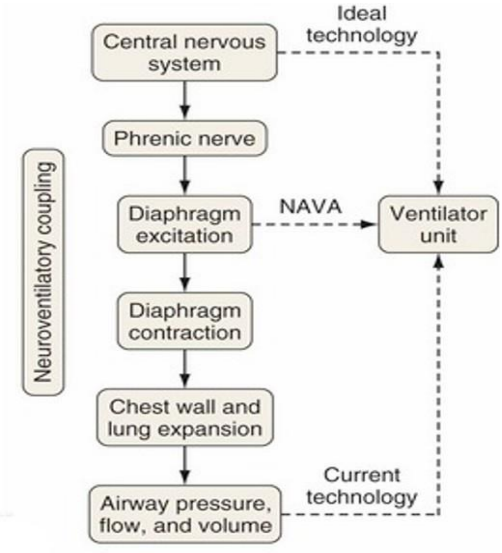


Figure 4: Diagram of a neuro-mechanical coupling and control of the ventilator (adapted from Sinderby et al 1999 and Brander & Slutsky2015).[100,131]

The amplitude of Edi waveform has been shown to be related to global diaphragmatic activation.[132] The Edi waveform represents the neural breathing pattern, such as neural inspiratory time, neural expiratory time and neural respiratory rate. It can be used to monitor patient ventilator interaction.[46,104,133,134] It can also be used to quantify the ventilator response delay in an assisted breath by comparing to the airway pressure waveform, i.e. inspiratory trigger delay, premature cycling off and cycling off delay, and can be used to detect other types of asynchrony, such as ineffective triggering, auto triggering and double triggering.[1,64,108]

Neurally Adjusted Ventilatory Assist can be delivered by invasive and non-invasive interfaces in all patient ages. However, NAVA cannot be used if the Edi signal is absent, insertion of an orogastric or nasogastric catheter is contraindicated, or ventilatory parameters are unacceptable. Because NAVA uses the Edi to control the assist, the assist is mostly delivered in synchrony and in proportion to neural inspiratory efforts. To control the ventilator, the efficiency of pressure generation depends on the NAVA level, and the gain factor which controls the amount of pressure for a given Edi. When the Edi remains constant, an increase in the NAVA level only increases the ventilator's relative contribution to the trans-pulmonary pressure.[66]

Setting the trigger in the NAVA, the assist is triggered by the initial increase in Edi. The NAVA is triggered by a deflection in Edi, not an absolute level of Edi. There are two inspiratory trigger functions in NAVA. The first principal function is the Edi signal, which should precede the pneumatic trigger function. The second function, which is a default function, is an airway pressure signal and inspiratory flow signal. To avoid inspiratory occlusions during triggering, if pneumatic triggering occurs (before Edi triggering), a pressure of 2 cmH_2O is delivered until the Edi appears. This event may occur when the filtering of the ECG or artifacts coincides with the beginning of the Edi, or the flow may be generated first by the inspiratory muscles. In this case, the ventilator is triggered by either change in Edi or flow, on a "first come, first served principle".[59,66]

In NAVA, the ventilator delivers airway pressure in proportion to the Edi. The Edi signal is updated every 16 ms, and it is multiplied by a proportionality constant known as the NAVA level (gain), which is used to increase or decrease the assist. The level is available from 0 to 15 µV and can be adjusted in steps of 0.1 $cmH_2O/\mu V$. The upper limits are applied during NAVA and can be adjusted; the default is 5 cmH_2O below the dial in limit. To set the NAVA level the operator adjusts the proportionality between the voltage and airway pressure to achieve ventilation goals and optimal ventilatory parameters, including level of inspiratory pressure support, tidal volume and respiratory rate.[67]

Inspiratory cycling off in NAVA is set when the Edi drops to 70% of the highest Edi value (Edi-peak/Edi-max). When the Edi peak value is low, cycling off occurs at lower percentages. The breath cycles off anytime peak pressure exceeds the predicted NAVA pressure by 3 cmH_2O. In the case of a long neural inspiration, there are time criteria for cycling off: 1.5 seconds in infants and 2.5 seconds in adults. Neurally Adjusted Ventilatory Assist may be considered a self-weaning mode, as when ARF improves the Edi amplitude decreases, and the airway pressure delivered will also decrease.[66]

2.4. Measurement of the treatment effects

Given the included studies are considered to have enough in common in their PICOs and study designs, a statistical approach for quantitative data synthesis was used. Meta-analysis is used to evaluate and summarize an overall effect size from two or more individual studies effect sizes (estimated as a weighted average effect size), the dispersion of effect size, the homogeneity/ heterogeneity of effect size (observed effect sizes) and the publication bias.[135]

The studies in this systematic review shared a similar population group, used similar intervention and were compared to a similar comparator. All studies also investigated head to head comparison of NAVA versus PSV and reported the PVD outcome measures in the same measurement instrument and scale, which measured AI%, NeuroSync index and ICU mortality. To calculate the indexes, the AI% group used a similar formula and in the NeuroSync index group used an identical formula. However, the included studies have two different study designs, the first group were RCTs (two studies), the second group were cohort crossover designs (15 studies).

A crossover design study may raise a concern about a carry-over effect, which could modify a physiological effect that influences the patient responses to the subsequent intervention. In the included studies, the wash out period in each study was considered reasonable practice. According one study that evaluated the time necessary to stabilize respiratory mechanics after changing the ventilator setting to PSV mode in COPD patients, six to eight breaths is required to stabilize their values.[136] This time required can be considered a minimum wash out period. According to Elbourne et al, if the parallel and crossover trials evaluate the same treatment (not discounting the possible presence of a carryover effect into consideration), and if the trial design is not based upon different therapeutic indications or clinical conditions which could alter the treatment effects, it is reasonable to combine parallel and crossover trials in a systematic review.[137]

The studies included in this systematic review were characterised by clinical and methodological heterogeneity i.e. participant clinical characteristics, IMV setting strategies in each mode, group of investigators, study design, quality of the studies, the extent of participant withdrawal numbers, and other covariates that might be known or not known to be related to the size of the effect. Therefore, each study expects to be similar but not identical. The meta-analysis model that accounts for this variation is a random effects model as it assumes that the true effect varies between studies and are normally distributed.[138] The random effects model of meta-analysis was used in the outcomes that have a greater number of studies, to statistically estimate the magnitude of individual study effect size and associated precision. For the outcomes that have a small number of studies i.e. the two RCTs that investigated AI% and mortality outcomes and two crossover cohort studies that investigated the NeuroSync index, the fixed effect model is recommended and considered appropriate. [139]

Furthermore, a statistical test in meta-analysis that provides information about heterogeneity, which are a Q statistic test with a *p* value, I^2, Tau squared (T^2) and Tau were evaluated.[135] When the heterogeneity of effect size presented in a moderate and high proportion of I^2, a subgroup/moderator analysis was conducted. Methodological differences in study design (cohort crossover and RCT), treatment duration and treatment measurement-time were assessed and clinical differences that could possibly impact on the effect size were assessed i.e. patient levels of consciousness by evaluating sedation practice in each study (sedated and non-sedated study groups). Other possible covariates/ moderators were not evaluated because there was limited availability of data from the primary study studies.

The following chapter, the systematic review method**,** outlines the inclusion criteria for the systematic review search strategy and assessment of methodological quality.

Chapter 3: Methods

Review objective/questions

As stated in Chapter One, the objective of this systematic review was to systematically review the best available evidence on the safety and effectiveness of NAVA compared with PSV in critically adult patients in ICUs. The safety and effectiveness are measured by less preventable harm or absence of preventable harm to the patients (lower or absence of PVD frequency and mortality) from using the interventions.[34]

The specific questions this review sought to address were:

- Does NAVA influence patient ventilator synchrony compare to PSV among critically ill adult patients on IMV support in an intensive care environment?
- What is the evidence of safety (PVD frequency and mortality) related to use of NAVA compared with PSV when used in critically ill adult patients in an intensive care environment?

3.1. Inclusion criteria

3.1.1. Types of participants

The review considered studies that included critically ill adult patients in all demographic groups with or without existing comorbidities, and with any cause of precipitating respiratory failure requiring partial assisted invasive mechanical ventilation via endotracheal or tracheostomized intubation in ICUs.

3.1.2. Types of intervention and comparators

The primary intervention of interest was NAVA with an optimal ventilatory support setting. If multiple levels of NAVA gain factor (level of assistance) were studied, they were defined as potentially suboptimal (low assistance), optimal (adequate assistance) and high (over assistance). The optimal setting of NAVA (examined by the authors and

as stated by the primary study authors) was considered and synthesized. If a study used only one group of setting parameters of NAVA and PSV, they are considered optimal settings in this regard.

The comparator was a standard conventional mechanical ventilation, which is defined as PSV. The pressure support ventilation used different levels of ventilator setting parameters such as levels of pressure support assistance, levels of ITS, levels of ETS and level of PEEPe. They can be defined as suboptimal (low), adequate (optimal), and high (over-assistance). The optimal level is the level that showed the lowest PVD events (AI% and NeuroSync index or patient ventilator asynchrony %), or the primary study authors stated it is the optimal setting. The optimal levels are classified based on available scientific evidence in the literature according to the primary investigator's reported data, and it is an arbitrary level.

3.1.3. Type of outcomes

The outcome measures for this review were modified from the original systematic review protocol.[112] The new revised systematic review protocol is provided in Appendix I. The major change was to reduce the (very large) number of outcomes of interest (from 9 to 2) to enable the project to be completed within the available resources and timeframe. For methodological appropriateness and clinical meaningfulness PVD frequency measured by AI%, AI>10%, NeuroSync index and PVA% and mortality, were included. Outcome data was extracted based upon the following descriptions.

1. Patient ventilator dyssynchrony frequency: It is detected by visual inspection of airway pressure, flow oesophageal pressure and Edi graphic waveform and by automated computer analysis of patient ventilator interaction. For calculation of dyssynchrony incidence by visual inspection of graphic waveforms, an asynchrony index formula was used[45], and for PVA the PVA% formular was used.[65] With automated computer analysis, the NeuroSync definition and calculation were used to identify and calculate the NeuroSync index.[140]
2. Mortality from all causes and from IMV related causes as reported by the primary study authors.

3.1.4. Types of studies

This review considered experimental and observational studies that examined the effectiveness of NAVA compared to PSV. Experimental study designs, including randomized controlled trials, non-randomized controlled trials/quasi-experimental studies; cohort studies were also considered.

3.2. Search strategy

The search was conducted in accordance with the Joanna Briggs Institute (JBI) methodology guidelines for a systematic review assessing the effectiveness of an intervention and therapy.[141] The suitability of the proposed review topic was determined by conducting a preliminary investigation of major electronic databases. Results of searches of the Joanna Briggs Institute Library of Systematic Review Protocols, the JBI Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, PubMed, PROSPERO and DARE databases showed that there had been no recently published systematic reviews on the same topic.

3.2.1. Search method

The search strategy was developed based upon a three-step process and was designed to find published and unpublished studies. No date restrictions were applied initially. An initial search of PubMed, EMBASE, and Cochrane CENTRAL was undertaken to identify keywords in titles and abstracts related to the PICO elements of the review questions. The initial keywords and terms included patient-ventilator interaction, patient ventilator asynchrony, Neurally Adjusted Ventilatory Assist, NAVA, invasive mechanical ventilation, artificial respiration and patient ventilator synchrony, asynchrony, and dyssynchrony.

A second search of each database was then conducted utilizing all identified free text and database specific index terms (Appendix II), ensuring as comprehensive a search as possible. When searching, consideration was given to each databases' unique indexing language to ensure all relevant indexing terms were identified.

Included in the search of international databases were clinical trial registries as well as the following international electronic databases: Cochrane (CENTRAL), CINAHL, Web of Science, EMBASE, PubMed and SCOPUS. A system alert for possible relevant new publications in each database was set by using their relevant indexing terms.

A third search of databases was conducted to ensure that all relevant studies were identified and to finalize a comprehensive and up to date search. This final search was limited to the English language due to unavailability of translation resources. This search filter including the terms human and year 2007 were used in this step of database search. The reason for this is that the first human experimental study with NAVA was published in 2007.[142] A final search was conducted to update the search to the 30th March 2018 for four databases including Cochrane, PubMed, ACOPUS and Clinical Trials registries and on the 6th of April 2018 for EMBASE. Details for the final databases searched are provided (Table 1).

Using citations that were identified based on keywords in abstract and titles, full papers were retrieved and scanned to determine whether inclusion criteria had been met. Finally, to ensure that all relevant studies were identified, the reference list of retrieved papers was scanned and a full text of included and excluded studies' reference list (1299 studies) also screened to identify any additional studies. Appendix II reports details of search strategies for each database and trial registry website. Results of database searching were managed using the bibliography software EndNote x8 (Thomson Reuters, USA, 2015).[143] The EndNote library created was used to facilitate screening of titles and abstract of citation to assess eligibility for the review.

3.2.2. Search results

The Following table displays numbers of items found in each electronic database from a final search in which 1078 items were retrieved.

Table 1: Database searched, including search dates, filter limit, and frequency of items found

Databases and Search	Filters and limits	Item(s) found
Cochrane (CENTRAL) 30.03.2018	Trial	95
EMBASE	No limit or filter	285
MEDLINE (PubMed) 30.03.2018	No limit/ filter	382
SCOPUS 30.03.2018	Date 2007 to Present (30.03.2018), subject area, humans, English journal, humans, journal, access type (open and others)	280
www.ClinicalTrials.gov 30.03.2018	Completed studies, adult and senior	35
Additional Resources Electronic database alert from each database and study reference reading	As per each database used (see Appendix II)	1

3.3. Assessment of methodological quality

3.3.1. Critical appraisal step

Quantitative studies were independently assessed by two reviewers (AP and DC) for methodological quality and validity to ensure transparency and minimize risk of bias prior to inclusion into the review.[30] The Joanna Briggs Institute critical appraisal tools designed to assess the internal validity and methodological quality of the studies were used to allow consideration of the extent to which each study had addressed the likelihood of bias in the study design, conduct and analysis. The two parallel RCT studies were assessed against the *Checklist for Randomized Controlled Trials* and 15 crossover studies were assessed using the *Checklist for Cohort Studies* (see Appendix III).

The critical appraisal step employed the JBI checklist for randomized controlled trials. It consists of 13 quality assurance questions that could be answered 'Yes', 'No', 'Unclear (U)' or 'Not applicable (NA)'. The checklist for cohort studies consists of 11

quality assurance questions. Quality criteria were developed around each of the appraisal questions to ensure consistency and transparency in interpretation between reviewers. A 'Yes' answer deemed that the study met the requirements of question, a 'No' meant it did not meet the requirements, an 'Unclear' indicated that insufficient study information had been provided to enable a conclusive decision about the inclusion, and a 'Not applicable' indicated non-discernible to assess by means of a reliable objective or subjective measurement tool. 'Yes' and 'Not applicable' answers were allocated a score of '1' while 'No', 'Unclear' were scored '0'. The explanation for given each answer provided in Appendix IV.

Tables 4 and 5 provide the critical appraisal scores of 17 included studies in question 11 for a cohort crossover study and question 12 for an RCT, which relate to the statistical analysis used. All studies were given a score of 1 in the critical appraisal assessment of statistical analysis questions.

Statistical analysis of included studies

Overall, the 17 included studies used appropriate statistical test models including normality tests, nonspecific null hypothesis tests, post hoc analysis and procedures for reducing family wise error rates and false discovery rates. The following is an overview of statistical procedures/tests that the included studies used to statistically analysed the outcomes that met systematic review outcomes.

Normality distribution test

Six included studies reported a normality assumption test with three models that included the Shapiro-Wilks test, Kolmogorov Smirnov test and D'Agostino test.[144-146] The Shapiro-Wilks test was used by one crossover study;[147] the Kolmogorov Smirnov test was used by four crossover studies;[1,20,148,149] and the D'Agostino test was used by one RCT.[10] In this group of studies, one crossover study provided AI% in median and IQRs) and the number of patients had AI>10%, but a statistical analysis was not performed for difference in these two outcomes.[106] In practice, the normality test was advised to be performed after a visual method test was done. The visual method included visual analysis of the frequency distribution (histogram), stem- and- leaf plot, boxplot and P-P plot etc.[146] The normality test is performed to provide the next step of an appropriate analysis model.

(i) Non-specific null hypothesis test

- A $\chi 2$ test is to be used with any number of variables to determine an association between two categorical variables. There are four assumptions needing to be satisfied: to be able to use this model samples must be independent, participants in each group have been randomly and independently selected, the classification categories in the distribution are mutually exclusive and exhaustive, and the sample size is reasonably large.[150] The study by Demoule et al 2016 used the $\chi 2$ test, as they considered the four assumptions were met, to evaluate an association between modes and mortality.[109]
- An analysis of variance (ANOVA) is used for normally distributed data. In this case, Two-way ANOVA with repeated measures was used with study phase as with-in subject and between subject factors (Mauri et al 2013: NAVA, PSV1%, PSV30%).[16] Two-way ANOVA with repeated measures also used to compare variables between two modes and the two levels of assist (Spahija et al 2010: NAVA-low, NAVA-high, PSV-low, PSV-high).[65] Two way ANOVA was used to compare each variable dataset (Terzi et al 2010: NAVA and PSV level 100, 120,140 and 160).[2] These studies satisfied criteria of the Two-way ANOVA repeated measures as the participants are the same in each group (crossover), participants were measured multiple times in each group and participants were subjected to more than one condition.
- As an alternative to ANOVA for non-parametric test with repeated measures, the Friedmann test was used by six studies,[21,46,140,149,151,152] to evaluate the difference between groups for matched datasets.[153] All studies evaluate two modes with multiple factors measured at different times except one crossover study evaluated three modes.[154]
- As an alternative to ANOVA for non-parametric test with repeated measures, the Friedmann test was used by six studies,[21,46,140,149,151,152] to evaluate the difference between groups for matched datasets.[153] All studies evaluate two modes with multiple factors measured at different times except one crossover study evaluated three modes.[154]

(ii) Post hoc analysis

When a non-directional hypothesis test reported that the null hypothesis is rejected, a post hoc analysis for each study was conducted. In one study, a mixed model analysis was used for repeated measures on each subject over time to evaluate an interaction between modes and levels of assistance after a two-way ANOVA was performed, and the null hypothesis was rejected. Each mode used 4 levels of assistance evaluated (NAVA-Edi, NAVA-IF, PSV). The AI % of each mode was reported in a graphic display.[155]

- The Wilcoxson signed rank test or Mann-Whitney test are basically the same. Both are used to compare two repeated measures in non-parametric data. The data required to meet four assumptions include dependent variable measures in the ordinal or continuous level, consisting of two categorical independent groups, the two samples have to be independent on observations of cases and a non-parametric distribution.[156] Five crossover studies used the Wilcoxon signed rank test to perform a post hoc pairwise comparison.[20,21,24,46,152] All studies investigated two modes (categorical data) and to meet the Wilcoxon signed rank test assumptions, they reported AI% (continuous data) and AI>10% (dichotomous data), except one study reported only AI%;[148] consisted of two categorical independent groups (NAVA vs PSV); had dependent observations (pre and post measurements); and had non-parametric data (reported median, IQR).
- The Mann-Whitney U test is sometimes called Wilcoxon Mann Whitney U test. It is used to compare two-separate unrelated (independent) groups and is a nonparametric alternative to a two-sample t-test.[157] Two of the included RCT studies used this test to evaluated continuous independent variables (AI% and mortality).[10,109]
- The Student-Neuman-Keuls test was used to perform pairwise comparison and step wise approach in three studies to identify significant difference.[1,65,140]
- Dunn's test was used in one crossover study to evaluate difference between modes in multiple comparisons, and it reported a NeuroSync index in three modes.[151]

- The Tukey test is used to identify where differences lie in multiple comparisons and to keep family wise error down.[158] One crossover study used the Tukey test for multiple comparisons to identify those differences which compared two modes with two conditions in PSV and reported AI% (Mean ± SD) when the Tukey test assumptions were met.[16]

(iii) Categorical variable statistical analysis

For analysis of categorical variables, two studies used a non-parametric test as following.

- The McNemar's test is used to identify whether there are any differences between a dichotomous variable between two related group (paired data).[153] It was used by one crossover study to evaluate AI>10% in the study of two modes of ventilators with five factors of study in each mode.[148]
- Fisher's exact test is a non-parametric test used when $\chi 2$ assumptions are not satisfied. It is used to evaluate an association and difference in two categorical variables.[153] Two crossover studies used it to analyse the number of participant that AI>10%.[22,152]

(iv) Family wise error rate/ false discovery rate

To control the family wise error rate in multiple comparisons, different studies used different procedures. The Bonferroni adjustment/ correction was used in two crossover studies [151,152] and *p* values adjusted according. To prevent over estimation of statistical significance in a small data set, Yate's correction was used in one crossover study.[20] It is used after a $\chi 2$ test is performed to evaluate an associations between two dichotomous variables (AI>10% in two modes).[159] In addition, Benjamini Hochberg was used by one crossover study to control false discovery rate.[160] A descriptive overview of statistical analysis is provided in Appendix VII.

Any disagreement that arose between the reviewers was resolved through consultation with the third reviewer (CL). Given there were limited studies that evaluated PVD frequency, a low threshold for methodological quality was used to include 15 cohort crossover studies into the review. All 15 studies scored 11 / 11 from

using the JBI critical appraisal cohort study checklist tool. There were two RCTs included in this review. The critical appraisal score of these two studies were 8/13 and 11/13, which was considered moderate to high quality. The following Table presents outcomes measured from each study that reported the systematic review outcomes.

Table 2: Studies by review outcome measures

Outcome Measures	Study
AI%	Ferreira 2017, Beloncle 2017, Di mussi 2016, Demoule 2016, Carteaux 2015, Schmidt 2015, Yonis 2016, Vaschetto 2014, Mauri 2013, Patroniti 2012, Piquilloud 2011, Terzi 2010, Colombo 2008
AI>10%	Ferreira 2017, Beloncle 2017, Costa 2017, Carteaux 2015, Yonis 2015, Schmidt 2015, Vaschetto 2014, Patroniti 2012, Piquilloud 2011, Colombo 2008
NeuroSync index	Doorduin 2015, Liu 2015
Mortality	Di mussi 2016, Demoule 2016
PVA%	Spahija 2010

3.3.2. Data extraction

Descriptive and outcome data was extracted from the included studies using the standardized data extraction tool from the JBI MAStARI presented in Appendix IV. The data extracted included specific details of intervention (NAVA) and comparators (PSV). These parameters include ventilator setting parameters that may cause PVD, i.e. levels of assistance, PEEPe, ETS, ITS, study dependent variable, constant variable setting, identical settings, NAVA gain and PS level (Appendix V). Data of demographic characteristics of included studies in the review are presented in Table 6, and demographic characteristics of participants in included studies presented in Appendix VI. A request for additional data was made to corresponding authors of the RCTs and the information requested was provided. Data provided by the study authors are detailed in Appendix VII.[2,4,25,59,65,109,148]

3.3.3. Data synthesis

Most included studies used the PVD calculation by Thille et al, 2006, p.1517.[45] Two studies used the NeuroSync index .[140,151] and one study used patient ventilator asynchrony %.[65] Of the 14 studies that used the Thille at al formula to calculate AI%, three studies identified AT, DT and IT;[20,149,152] two studies identified DT and IT;[2,147] the other four studies identified AT, DT, IT and premature cycling.[1,10,16,46] However of these four studies, two studies also identified cycling off delay/ delay cycling.[10,46] Considering there were two or more studies that measured PVD events by identifying similar defined dyssynchrony events and measurement scale, and two RCTs investigated mortality outcomes, pooling data for statistical meta-analysis using Comprehensive Meta-Analysis software (CMA) was considered appropriate and clinically meaningful. Therefore, the finding of AI% and AI>10% were meta-analytic in a random effects model when the number of studies is more than two. In the random effects model, it assumes that the true effect size varies, and the summary of effect size is an estimation of the mean of the distribution of effect sizes. The NeuroSync index in two crossover studies, the AI% and ICU mortality in two RCTs were meta-analytic in a fixed effects model. Under the fixed effect meta-analysis, it is assumed that all studies have one true (common) effect size, and all observed dispersion indicates sampling error. Meta-analysis is used to compute a summary effect. The Z statistic test is used to test for significance tests of the weight average effect size. The null hypothesis for the difference is zero (that d is 0.0), and for the ratio is one. The *p* value is less than 0.05 when 95% CI does not include the null hypothesis.[161] The patient ventilator asynchrony percentage was written in a narrative summary.

- **Meta-analysis method**

Sixteen studies presented data suitable for inclusion into meta-analysis (13 studies for AI%, 10 studies for AI>10%, two studies for NeuroSync index and two studies for mortality). One study was reported in narrative format as it was not able to be combined in meta-analysis. Of those studies reporting AI% and AI>10%, 10 studies reported both index outcomes. Required data were provided by seven study authors (Appendix VII) and required paired comparison *p* values were calculated for seven studies (Appendix X). MedCalc Software was used to calculate significance values for the studies that

did not report *p* values.[162] The prediction interval was calculated using Excel program, with a formula from the CMA Software.[163]

When the studies reported the continuous outcome (AI %) in median and IQR, the numbers were approximately estimated to be mean ± SD by using formulas

$\bar{X} \approx \frac{q_1 + m + q_3}{3}$, and $S \approx \frac{q_3 - q_1}{1.35}$. which were recommended by Wan et al 2014,when 'q1' is the first quartile, 'q3' is the third quartile, 'm' is median, and 'n' is the sample size are available.[164] The first formula is from wan et al 2014 (p. 6) estimation, and the second formula was recommended by the Cochrane Handbook;[165] Outcome data extraction and calculation details are provided in Appendix X.

For pooled estimation of overall effect size in continuous outcomes, the difference in means, 95% CI and the standard error of the difference were calculated, and for dichotomous data, the treatment effects were reported in odds ratios (OR) and 95% CIs. The computational meta-analysis of continuous data is performed by using standardized mean difference (SMD) which is an unbiased effect size parameter, Hedges' g.[161] Hedges' g is used because it is recommended to use in less well-known measurement and when the different studies use different instruments to assess the outcomes. In this case, the measurement and calculation of AI% in each study used a few (two to five) of seven defined patient ventilator asynchrony characteristics (see Table 6), so it can be stated that included studies used the same measurement index but calculated differently. Therefore, it is more meaningful to use the standardised mean differences in estimating the summary of effect sizes. The Q hypothesis is 'all studies share a common effect size'. Of any observed Q with a conventional alpha set 0.05, if the *p* value less than set alpha, the null hypothesis is rejected. Prediction intervals were calculated in meta-analysis that used a random effects analysis. When *p* value of Q statistic test is significant, the prediction intervals were calculated. These numbers shows how the true effects are distributed around the mean effect size.[161]

Chapter 4 outlines the results, which includes description of the search results, included studies, mythological quality, and provides an overview of included studies, study characteristics, intervention types, outcome measures and methodology of measurement and outcome of interest. The summary of systematic review findings is presented in the final section.

Chapter 4: Results

4.1. Description of the included studies

Seventeen studies were included in this review. These are described in Table 6. Each individual study involved a sample size of 10 to 128 patients. A total number of 398 patients were recruited. Of these, 46 patients were unable to complete the study that measure AI% (38 patients in RCTs and eight patients in crossover studies). These eight patients were excluded from the studies that measured both AI% and AI>10% in crossover studies, and 38 patients were excluded from the RCT studies that measured AI%. Thirteen patients were withdrawn from the study that reported the ICU mortality.

Three hundred and fifty-two patients from 17 included studies provided 576 datasets which were evaluated and synthesized for PVD frequency. One hundred and fifty-three datasets from two RCTs were evaluated for ICU mortality. Only one study factor/ condition (level of assistance, ETS, NAVA gain, PS level and PEEPe) that provided the lowest PVD frequency (lowest AI%, lowest AI>10% event and lowest NeuroSync index) from intervention and comparator in each included study was considered for inclusion in the data synthesis, and missing datasets that the primary study authors did not report were not included.

Data synthesis for mortality was performed in 153 participants from two parallel RCTs. Of these two RCTs, one study stated that the outcomes were analysed with intention to treat (ITT).[109] To resolve the 25 missing datasets, the investigators performed a simulation by using a predictive mean matching method and reported a mortality outcome identified in 128 patients (NAVA; n=62 and PSV; n=66). The AI% was reported in 103 datasets (NAVA; n=53, PSV; n=50). The other eight missing datasets were from six crossover studies. Reasons for excluded patients from the primary studies are provided in the following table, Table 3.

Table 3: Reasons for exclusion participants from the primary study

Study	Reasons for dropout	
	NAVA	PSV
Di mussi (2016)[10]	Seven out of 20 patients did not complete the protocol according to the decision of attending physician. Two patients lost Edi-pneumatic synchrony, and five patients had the Edi signal persistently lower than the Edi trigger threshold.	Six out of 18 patients did not complete the protocol due to the decision of the attending physician. Two patients had persistently high respiratory rate, and four patients had a persistently low respiratory rate.
Demoule (2017)[109]	For technical reasons ventilator data collection failed in four patients.	For technical reasons, ventilator data collection failed in six patients.
Patroniti (2012)[147]	One patient was excluded from the analysis because unable to tolerate NAVA level 3, 4 and 5 $cmH_2O/\mu V$ and PS 16 cmH_2O.	
Vaschetto (2014)[152]	Two patients dropped out, one had hypotension and one was agitated.	
Piquilloud (2011)[1]	Three patients were excluded, one patient had neuromuscular disease, and two patients had un-normalized Edi during PSV.	
Colombo (2008)[22]	Two patients were excluded because of Paw-peak > 40 cmH_2O during NAVA 150% (NAVA-high assistance).	

4.2. Search results

A first comprehensive search of electronic databases followed the outline search strategies documented in Appendix II. The initial search of seven databases (Cochrane: CENTRAL, CINAHL, EMBASE, MEDLINE: PubMed, SCOPUS, Web of Science and ClinicalTrials.gov on 31st of May 2015 found 687 articles, and an email alert from six databases were set post initial search to receive potential relevant studies. All abstracts and available full texts of these articles were screened and assessed for eligibility. The potentially relevant study references were also screened from eight crossover studies,[1,2,16,22,23,26,65,147] which met PICO criteria and investigated PVD. The email system alert provided the author possible relevant studies being published. It identified identical published studies that provided by the final database search. a further nine studies in addition to those from the initial comprehensive search met inclusion criteria .[9,10,20,21,24,25,46,140,148] The final comprehensive search, conducted on the 30th March 2018 in Cochrane: CENTRAL, EMBASE, MEDLINE: PubMed, SCOPUS, and ClinicalTrials.gov and in EMBASE on the 6th April 2018, retrieved 1,077 potentially relevant articles/studies, plus an additional study from reference screening[140] (Figure 5). Six hundred and twenty-one articles were screened after

duplicates were removed. Four hundred and eleven studies were excluded based on review of titles and abstracts, and 210 studies with full texts were assessed for eligibility. A further 193 studies were excluded as they did not meet the inclusion criteria. Seventeen studies were analysed for methodology quality as per the revised systematic review protocol and included in the review, and all were subsequently included in the systematic review. The following PRISMA diagram outlines the study selection process of the final search.

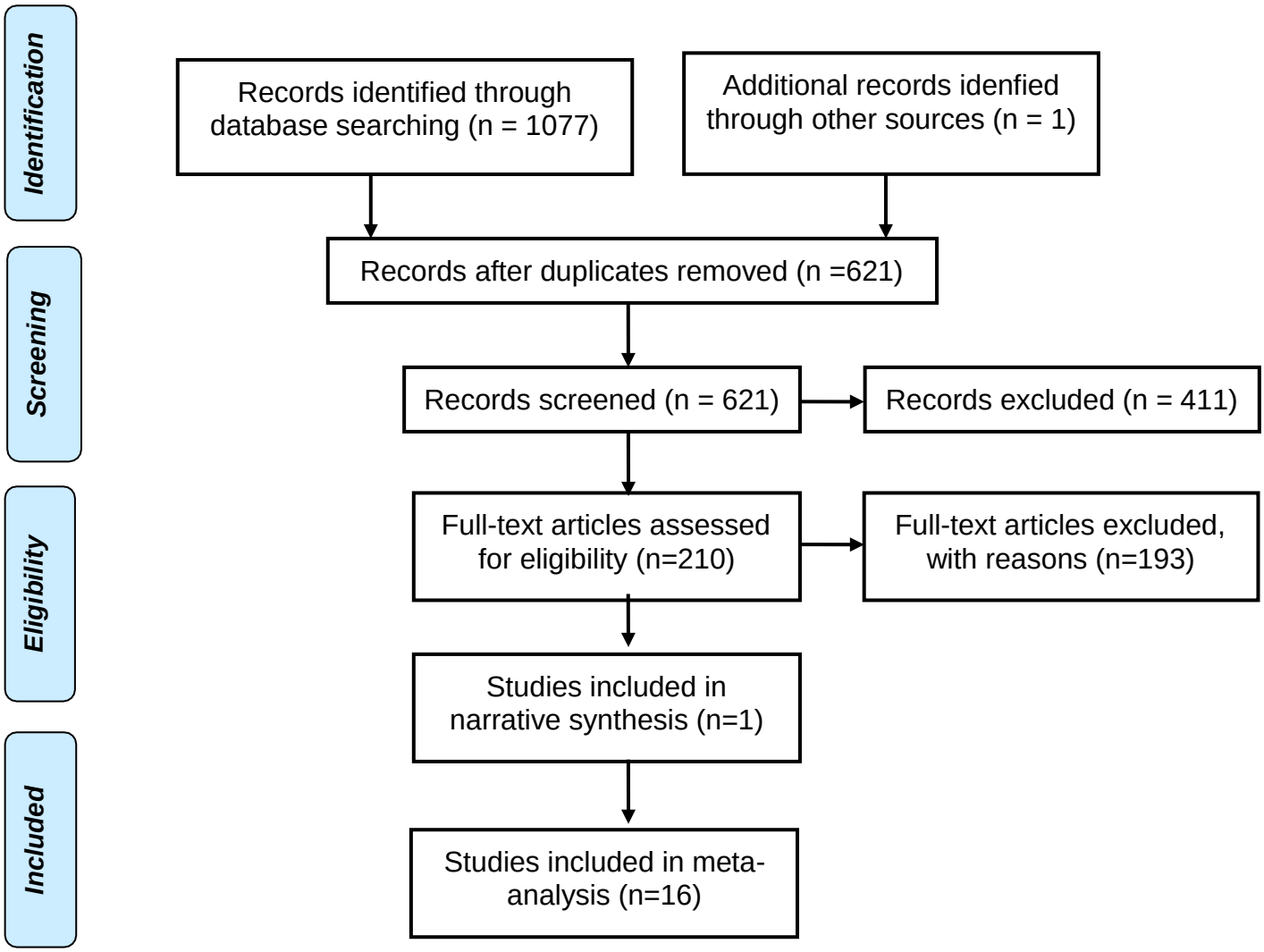


Figure 5: PRISMA flow diagram outlines of study selection and inclusion process.[166]

4.3. Methodological quality results

The cohort studies included in this review were rated as moderate quality, and the randomised controlled studies were rated as moderate to high quality as per critical appraisal checklist tool.[167] The appraisal scores of the 17 included studies are presented in Table 4 and Table 5.

Table 4: Critical appraisal score for randomized controlled trials meeting eligibly criteria as per systematic review protocol

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
Di mussi (2016)[10]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	8/13
Demoule (2016)[109]	Y	Y	Y	U	N	Y	Y	Y	Y	Y	Y	Y	Y	11/13

Table 4 in the study by Di mussi et al 2016, it was unclear in the randomised method and the concealment allocation method and overall blinding. Question 1, 2, 4, 5 and 6 were marked as unclear because there was no description of the required details reported. Similarly, there was no details given whether participants were blinded to the treatment assignment (Q4) in the study by Demoule et al 2016.

Table 5: Critical appraisal score for cohort studies meeting eligibly criteria as per systematic review protocol

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Beloncle (2017)[21]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Ferreira (2017)[24]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Costa (2017)[148]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Carteaux (2016)[46]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Schmidt (2015)[149]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11
Yonis (2015)[20]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Liu (2015)[140]	y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Doorduin (2015)[151]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11
Vaschetto (2014)[152]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11
Mauri (2012)[16]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11

Table 5: Critical appraisal score for cohort studies meeting eligibly criteria as per systematic review protocol

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Patroniti (2012)[147]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11
Piquilloud (2011)[1]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11
Terzi (2010)[2]	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	Y	11/11
Colombo (2008)[22]	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11

Q= question= yes, N=no, U = unclear and NA= not applicable. For each yes and NA 1 point accrues.

Table 5 in question 6 the score was given one mark because it could be considered that the question may be irrelevant with this group of patients who required this life support equipment and may not be applicable to the study design. To the author's knowledge there is no mode of ventilator has been justified and provided support to patient with perfect synchrony. For question 10 if there was no drop out in question nine, this question was considered not applicable. However, when there was a drop out, the authors simply excluded the patients from the studies or excluded the patient data from analysis.

Finally, 17 studies met the systematic review protocol criteria for inclusion. These 17 studies were assessed and appraised for methodological quality by two authors (AP and DC). All studies were included.

4.4. Overview of included studies

Studies were conducted on four continents: 13 studies in 24 ICUs of 14 European countries; France [2,20,46,109,149] Italy [10,16,22,147,148,152] Netherlands;[151] Switzerland and Belgium); [1] two studies in North America from Canada [21,65] one study from South America from Brazil [24] and one study from Asia, China [140] The studies were conducted in 28 ICUs, one study was conducted in 11 ICUs (six medical ICUs,[109] four medical and surgical ICUs and one surgical ICU did not specify the sites were a university setting), and one study conducted in two ICUs (both in medical surgical ICU),[1] other 15 studies were conducted in a single ICU. Of these 28 ICUs, that were reported participants were recruited from a variety of ICU including 10 university ICUs, 15

medical ICUs, nine medical/surgical ICUs, two general ICUs, one surgical ICU and one trauma/ medical/ surgical ICU.

Of these primary studies, the authors examined PVD frequency in a group with different aetiologies of ARF that identified as ARDS patients ,[2,16,151] COPD patients,[1,140] and the other 12 groups were a mixture of medical/surgical, trauma/ medical/ surgical and surgical patients. An overview of the 17 included studies characteristics is provided in Table 6.

4.4.1. Study characteristics

Of the 17 included studies, 15 were cohort crossover studies, and two were RCTs. A total of 13 studies investigated AI% (two RCTs and 11 crossover studies) and 10 crossover studies investigated AI>10% (Table 6). Of the 17 studies, nine studies investigated both AI% and AI>10%, four studies investigated only AI%, one study investigated only AI>10%, two studies investigated NeuroSync index, and one study investigated PVA%. Two parallel RCTs from 17 included studies investigated AI% and mortality. Fourteen studies used the Thille et al 2006 formula as reference to calculate AI%.[45] Two studies used NeuroSync index formula and one study used PVA% formula. The studied times investigated PVD events in the crossover studies ranged from 5 minutes to 23 hours (one study did not report duration of the treatment)[2] and the measurement time for PVD frequency was from 3 minutes to 30 minutes. One study measured for 100 breaths rather than time in minutes.[65] Intervention time (investigated PVD events in the parallel RCT studies) was 48 hours in duration and that record/ measurement time was 80 minutes in one study[109] and 120 minutes another study[10].

All studies used Servo-I ventilators except one study which used a modified Servo-300.[65] The Edi, Paw, flow graphic wave forms were used to identified PVD events. There was only one study where the person analysing the waveform tracings was blinded to the participants.[2] One study concealed the treatment by partially covering the ventilator screen to blind the bedside clinicians. [24]

Fifteen studies used V_T and/or Paw or mean airway pressure or Edi to set an identical level of assistance in both modes. Seven studies used both V_T and Paw [2,20,22,65,109,140,151] three studies used Paw;[1,21,24] two studies used only V_T.[10,16] Two studies used V_T and Edi;[148,152] and one study used V_T and mean airway pressure.[149] Two studies did not report how identical levels of assistance were set in both modes .[46,147] The studies reported that the PVD frequency was altered by adjusted ventilator parameters such as ITS, ETS, PEEPe, VT and PS. All studies reported setting ITS to avoid auto trigger in both modes and optimize an effective trigger, except in the study did not report in NAVA. [22] Ten studies reported setting PEEPe which ranged from median (IQR) 4 (4-5) to Mean ± SD 9.5±3.5 (see Appendix V). External positive end expiratory pressure settings were not reported in seven studies [16,46,148,151,152] Of these, one reported unmodified PEEPe during a study and another one reported adjusted PEEPe to PEEPi. One study investigated the effect of levels of PEEPe to NeuroSync index,[140] one study investigated levels of ETS settings in both modes affecting AI%,[16] and one study investigated an additional PS to NAVA and PSV setting that affected PVA%.[65] Ventilator setting strategy details are provided in Appendix V.

Recruited participants were mostly a medical patient, the study's primary study authors reported a variety of aetiologies of acute respiratory failure, and these were separately identified as 113 acute respiratory failure with respiratory causes (intra-pulmonary), 42 extra-pulmonary, 46 ARDS, 27 post-operatives, 33 COPD, 37 surgical and trauma, 11 pneumonias and 32 other types. The mean age of participants ranged from (mean ± SD) 58.9 ±15.89 to 78.8 ± 8.6 years with 200 males and 111 females. Four studies, which recruited 69 patients, did not report sex. The number of IMV days at recruited time ranged from (mean ± SD) 3±2 days to 23± 17 days. Participant demographic characteristics details are provided in Appendix VI.

A total of nine studies reported sedating of patients.[2,10,22,109,147,152] Three studies did not report a sedation scores and did not report whether patients were sedated [1,21,24], three study reported patients were not sedated, [16,20,65] and one study reported recruited patients who were sedated and non-sedated.[10] There was a group of

patients in five studies reported to have Richmond Agitation Sedation Scale (RASS) scores ranging from -5 (un-rousable to stimulus) to 4 (combative),[10,16,46,109,151] a group of patients in six studies had Ramsey Sedation Scale (RSS) scores ranging from 2 (cooperative, orientated and tranquil) to 4 (brisk response to stimulus),[2,22,140,147,148,152] and a group of patients in one study used a Bispectral index (BIS) titrated sedative agent dose to achieve a target level of consciousness.[152] The sedative agents used in the reported studies were propofol, midazolam, fentanyl and remifentanil. Details of sedation scores and sedative agents used are provided in Appendix VI.

4.4.2. Intervention types

All 17 studies investigated NAVA compared to PSV. Of 15 crossover studies, the primary study authors investigated not only two modes (NAVA and PSV), but some studies also investigated other modes that included PCV and PAV. The investigators also investigated multiple conditions(factors) in each mode. Of the 15 crossover studies, 13 studies compared NAVA to PSV, and two studies investigated three modes, one study investigated NAVA, PSV and PCV ,[151] one study investigated NAVA with PSV and PAV. [149] Of these, 13 crossover studies evaluated between two modes, nine studies evaluated two modes with multiple factors/conditions (levels of ventilatory support) [2,16,21,22,46,65,140,147,152] and four studies evaluated two modes with each mode assumed to have optimal ventilatory setting parameters.[1,20,24,148] Ventilator setting strategies and numbers of study factors/ conditions are provided in Appendix V.

As per the systematic review protocol, only NAVA and PSV outcome data were analysed and the AI%, AI>10%, NeuroSync index and PVA% from the optimal ventilatory setting (arbitrary scale identified by the outcomes that had the lowest number of PVD frequency) were used. Ventilator settings in all studies (ITS, ETS, PEEPe, V_T, Paw, PS, NAVA gain, FiO_2) were assumed to be optimal in each mode to meet individual patient respiratory demands. These settings were not altered during the study unless they were a factor in the study. To set the ventilatory support in both modes, the primary study authors set Paw and/ or V_T to get an identical level/ number. The factors that the primary study authors investigated were level of assistance (15 studies), PEEPe,[140] ETS,[16] assist level plus additional PS [65] and the effects of sedative agents and sedation level on the patients who were ventilated by each mode.[148,152]

4.4.3. Outcome measures and methodology of measurement

All studies used Edi, flow, Paw-graphic waveforms to identify PVD frequency, these were acquired from the ventilator monitor and transferred to the computer by using dedicated software. These patient data (graphic-waveforms) were analysed off line. These data were then used to calculate the AI% or NeuroSync index or PVA% by using different methods of identification and calculation. Of the 17 included studies, 14 used the AI% formula and two studies used the NeuroSync index formula,[140,151] and one study used PVA% formula.[65] Details of methodological of measure outcomes, calculation of PVD frequency and what PVD events each study measured are reported in Table 6.

Table 6: Included study characteristics

Study/Study design	Setting	Number of participant / drop out	Duration of intervention	Duration of measurement	Patient ventilator dyssynchrony event measured	Asynchrony index calculation
Costa (2017)[148] Crossover cohort	post-operative ICU of the Catholic University of Rome, Italy	13/0	25 min	5 min	IT, DT and AT	AI = total number of asynchronous events divided by the number of triggered and not triggered breaths
Ferreira (2017) [24] Crossover cohort	ICU of a university hospital in São Paulo, Brazil,	20/0	30 min	30 min	IT, DT, AT, cycling delay and premature cycling	AI= the number of cycles with asynchrony / the number of monitored neural cycles x100
Belonecle (2017)[21] Crossover cohort	Medical/surgical ICU of St Michael's hospital in Toronto, Canada,	11/0	10 min	5 min	IT, AT, DT, delayed cycling and premature cycling	AI= sum of 5 types of major asynchrony/ MRR+ IT x 100
Demoule (2016)[109] Parallel RCT	11 hospitals / centres in ICU in France	Investigated PVD: NAVA:62/9 (53) PSV:66/16 (50) Investigate mortality: NAVA:62/0 PSV:66/0	NAVA: 6.0 (3.0–12.5) days PSV: 8.0 (5.0–13.0) days	80 min (20min from 12, 24, 36 and 48 hr from enrolled)	IT, DT, AT, premature cycling and late cycling	AI= number of asynchrony events/total respiratory rate (ventilator cycles + wasted efforts) × 100.
Di Mussi (2016)[10] Parallel RCT	ICU of the University of Bari Academic Hospital, Bari, Italy	NAVA:20/7 (13) PSV: 18/6 (12)	48 hr	120 min	IT, DT, AT, premature cycling and short cycling,	AI= total number of asynchronies /MRR+ missed effort x100
Carteaux (2016)[46] Crossover cohort	Medical ICU of The Henri Mondor University Hospital Créteil, France.	11/0	5 to 10min	3 min	IT, DT, AT, premature cycling, and delayed cycling	AI (%) = (number of asynchronies/ [ineffective breaths + ventilator cycles]) x100.[168]
Doorduin (2015)[151] Crossover cohort	ICU of the Radboud University Medical Centre, The Netherlands	12/0	30 min	5 min	Automated computer algorithm detects error between Edi and Paw. PVD events defined as a trigger error, cycling off error, IT, DT and AT.	NeuroSync index calculated by averaging the errors for all breaths per patient per mode.[151]

Table 6: Included study characteristics

Study/Study design	Setting	Number of participant / drop out	Duration of intervention	Duration of measurement	Patient ventilator dyssynchrony event measured	Asynchrony index calculation
Liu (2015) Crossover cohort	General ICU teaching hospital affiliated with Southeast University in China.	12/0	12 min	3 min	Automated computer algorithm for all defined PVD events: early and late trigger, early and late cycling off, AT, and IT	The NeuroSync index was calculated by averaging the errors for all events/total breath.[69,140]
Schmidt (2015)[149] Crossover cohort	ICU of Sorbonne University, Paris, France	16/0	30 min	10 min	IT, AT and DT	AI-Thille AI formula[45] = number of asynchrony events/total respiratory rate (ventilator cycles +wasted efforts) × 100
Yonis (2015)[20] Crossover cohort	ICU of Rangueil Hospital, France	30/0	23 hr	25 min	IT, AT and DT	AI= total number of asynchrony events/ numbers of Edi signals x 100.
Vaschetto (2014)[152] Crossover cohort	ICU of the University Hospital of Maggiore Della Carità, Novara, Italy	16/2	25 min	5 min	IT, AT and DT	AI= ITI=IT breath/Total breathsx100; absent of DT and AT Thille (2006),[45] Colombo (2008)[22] and de Wit (2009) formulas were used.[56]
Mauri (2013)[16] Crossover cohort	ICU of San Gerardo Hospital, Monza, Italy	10/0	30min	5 min	IT, DT, AT, and premature cycling	AI-Edi = (flow- pressure and Edi based asynchrony events/ Edi RR x 100; Edi Thille= used Thille formula[45]
Patroniti (2012)[147] Crossover cohort	ICU of San Gerardo Hospital, Milan, Italy	15/0	10 min	5 min	IT and DT	AI= Number of asynchrony events (IT and DT/ total RR (MRR and IT) x 100
Piquilloud (2011)[1] Crossover cohort	Medical and surgical ICUs	25/3	20 min	20 min	IT, AT, DT, Cd and premature cycling	AI= Number of asynchrony events/ MRR+ IT x 100

Table 6: Included study characteristics

Study/Study design	Setting	Number of participant / drop out	Duration of intervention	Duration of measurement	Patient ventilator dyssynchrony event measured	Asynchrony index calculation
	of two university hospitals in Geneva, Switzerland and Brussels, Belgium					
Terzi (2010)[2] Crossover cohort	Medical ICU of the university hospital in Caen France	11/0	NR	5 min	Wasted effort(IT) and DT	AI= IT+DT/ Edi RR x 100
Spahija (2010)[65] Crossover cohort	Critical care unit, Sacre´ Coeur Hospital, University of Montreal, Canada	14/0	10min	100 breaths	Tdi and Cd	Ventilator asynchrony=Sum of Cd and Tdi per breath, expressed as % of total breath duration
Colombo (2008)[22] Crossover cohort	ICU, the Azienda Ospedaliera Maggiore della Carita, Novara, Italy	16/2	20min	5 min	IT and DT	(IT+DT÷MRR+ IT) x 100 Thille2006& Chao1997

ICU: intensive care unit, min: minute, PSV: pressure support ventilation, NAVA: Neurally adjusted ventilatory assist, PCV: pressure-controlled ventilation, PAV: proportional Assisted Ventilation, NR: not report, IT: ineffective trigger, DT: double trigger, AT: auto trigger: trigger delay, Cd: cycling off delay, Tdi: inspiratory trigger delay, MRR: mechanical respiratory rate, Edi RR: Electrical activity of diaphragmatic respiratory rate.

4.5 Outcomes of interest

The systematic review outcomes of interest are patient ventilator dyssynchrony frequency and mortality from all causes and from IMV related causes. The patient ventilator dyssynchrony frequency outcomes are categorized into AI%, AI>10%, NeuroSync index and PVA%. The mortality in the studies compared PSV with NAVA which reported PVD frequency is synthesized and reported in odds ratio and as reported by the study authors.

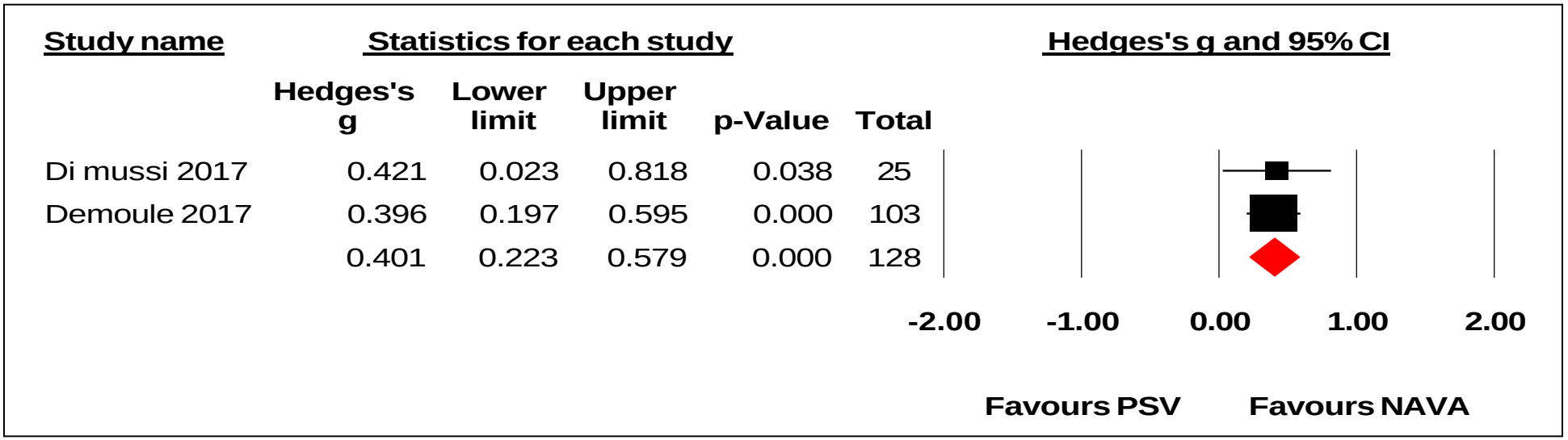
4.6. Summary of systematic review findings

4.6.1. Asynchrony index (%)

There were 13 studies that reported on the AI%. The individual study effect size and a summary estimate of effect size of SMDs are displayed in the forest plot of meta-analysis fixed effect, random effects and mixed effects as appropriate. A total of 13 studies were included in the AI% analysis outcome.

Figure 6 displays the fixed effect meta-analysis of summary effect size from two RCTs, which compared the effects of ventilator modes (NAVA versus PSV) on AI%. Both studies' populations were sampled from a group of 12 medical and surgical ICU settings from two countries in Europe (France and Italy).

- **Meta-analysis of asynchrony index (%) from randomized controlled trials**

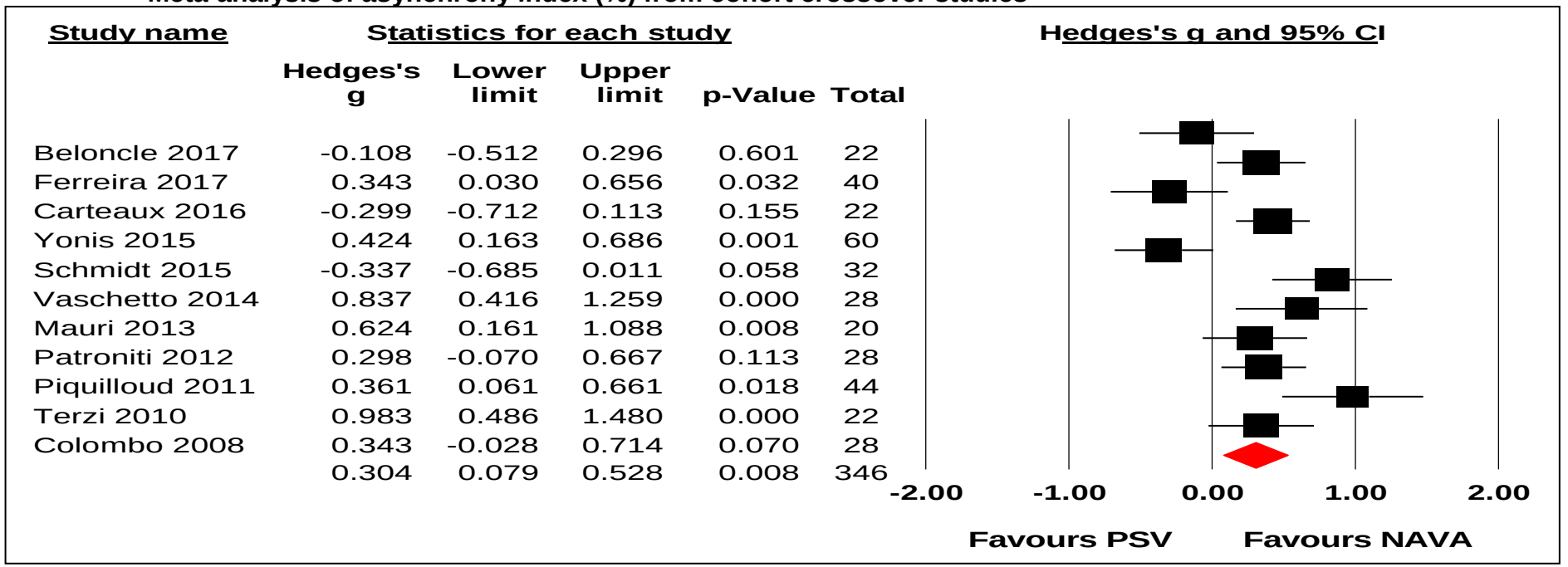


Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df(Q)	P-value	I^2	Tau-squared	Standard - error	Variance	Tau
0.401	0.091	0.008	0.223	0.579	4.415	0.000	0.012	1	0.914	0.000	0.000	0.036	0.001	0.000

Figure 6: Meta-analysis fixed effect of two RCTs depicts the pooled data of an estimated size SMD 0.401, 95% CI: 0.223 - 0.579, Z value 4.415, p=0.000, which is a statistically significant difference in reduction of AI% in the NAVA interventions compared with PSV.

The analysis is based on two studies that evaluated the effect of NAVA compared with PSV in optimizing patient ventilator synchrony by using AI% on partial assist invasive mechanical ventilated critically ill mixed medical and surgical patients in 12 ICUs. In each study the patients were randomly assigned to either NAVA or PSV, and the researchers recorded their PVD events intermittently during 48 hours of treatment with a PVD event measurement-time of 80 minutes[109] and 120 minutes. [10] The effect size is the SMD. The difference in means is 0.401 with the Z-value for testing the null hypothesis (that *d* is 0.0) being 4.415 and an associated *p* value of 0.000. On average, patients who were ventilated with the NAVA mode had an AI% nearly one half a standard deviation lower than those ventilated with PSV mode. The 95% confidence interval of the difference in means is 0.223 to 0.579, which indicates that the mean effect size could fall anywhere between this range, and it does not include an effect size of zero. Furthermore, there is no evidence of variation of true effect. In this case the Q value is 0.012 with 1 df, and *p* value is 0.914, which fails to reject the null hypothesis that the true effect size is identical in all studies. The I^2 at 0.00% indicates that there is no evidence to suggest that there is a proportion of the observed variance reflecting differences in the true effect sizes rather than sampling error. Tau and T^2 are zero. This meta-analysis of effect size provides strong evidence for rejecting the null hypothesis that is the mean true effect is not zero. The forest plot display provides evidence to suggest that NAVA has a better effect in reduction of AI% than PSV.

- **Meta-analysis of asynchrony index (%) from cohort crossover studies**



Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df(Q)	P-value	I^2	Tau-squared	Standard -error	Variance	Tau
0.304	0.115	0.013	0.079	0.528	2.650	0.008	41.415	10	0.000	75.845	0.107	0.066	0.004	0.327

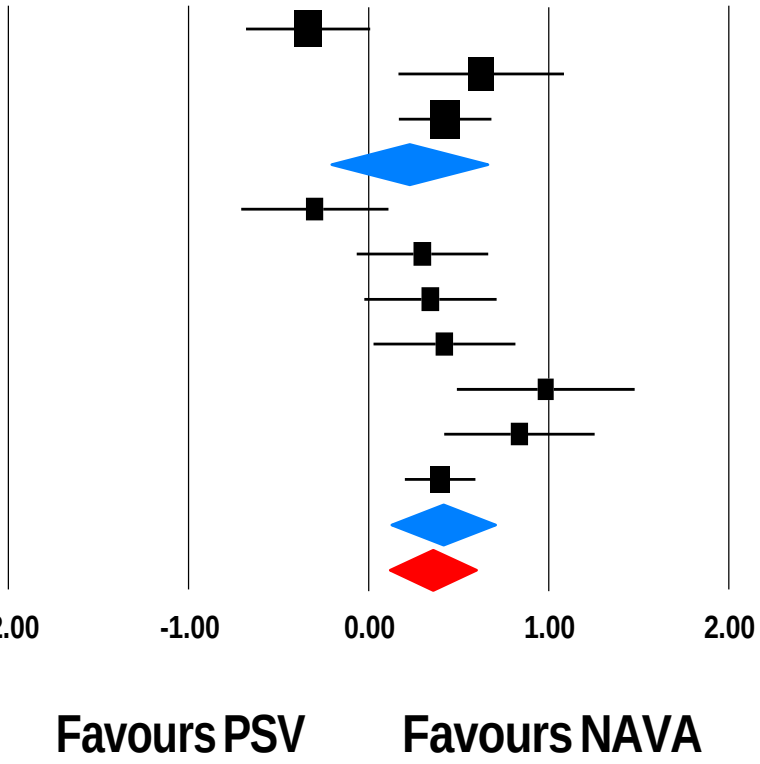
Figure 7: Meta-analysis random effects of 11 cohort crossover studies depicts the pooled data of an estimated size SMD 0.304, 95% CI: 0.079 -0.528, Z value 2.650, p=0.008, which is a statistically significant difference in reduction of AI% in the interventions compared NAVA with PSV.

The above analysis is based on 11 cohort crossover studies that evaluated the effect of NAVA compared with PSV in optimizing patient ventilator synchrony by using an AI% on partial assist invasive mechanical ventilated critically ill mixed medical and surgical patients in 12 ICUs in four European countries, one North America and one South America country. These studies relied upon convenience sampling of patients assigned to either NAVA or PSV, and the researchers recorded their AI% during the treatment duration (10 minutes to 23 hours) with the measurement time from 5 minutes to 25 minutes. One study did not report treatment time. [2] The effect size is the SMD, which is 0.304 with the Z-value for testing the null hypothesis is 2.650 and associated *p* value of 0.008. It suggests a statistically significant difference in effect size. On average, patients who were ventilated with NAVA mode had an AI% one third of a standard deviation lower than those ventilated with PSV mode. The 95% confidence interval is 0.079 to 0.528, which indicates that the mean effect size could fall anywhere between this range, and it does not include an effect size of zero. Furthermore, there is some evidence of variation true effect. In this case the Q value is 41.415 with 10 df, and *p* value is 0.000, in which the null hypothesis is rejected, so the true effect size is non-identical in all studies. The I^2 is 75.854% indicating that there is evidence to suggest that there is a high proportion of the observed variance that reflects differences in the true effect sizes rather than sampling error. Tau squared is 0.107, and the prediction interval is -0.4802 to 1.0882; this would suggest that in some 95% of all populations, the true effect size will fall in this range. The pooled estimate of effect provides evidence to suggest that NAVA has a better effect in reduction of AI% than PSV.

Although the overall effect size is significant, the high I^2 indicates substantial variability among the studies. When I^2 is 25% (arbitrary) and higher, a combined effect size from meta-analysis should not be interpreted as meaningful.[135] Therefore, the combined effect size of this meta-analysis is considered less meaningful. To investigate and quantify the extent of inconsistency findings across the studies a subgroup/ moderator analysis was conducted.[167] This investigation aims to evaluate the influences of specific clinical differences (Figure 8) and methodological differences between the studies (Figure 9 and Figure 10).

- **Meta-analysis of asynchrony index (%) of randomized controlled trials and cohort crossover studies: effects of clinical differences on heterogeneity (I^2)**

Group by Sedation	Study name	Statistics for each study				
		Hedges's g	Lower limit	Upper limit	Total	p-Value
Non sedated	Schmidt 2015	-0.337	-0.685	0.011	32	0.058
Non sedated	Mauri 2013	0.624	0.161	1.088	20	0.008
Non sedated	Yonis 2015	0.424	0.163	0.686	60	0.001
Non sedated		0.225	-0.208	0.659	112	0.308
Sedated	Carteaux 2016	-0.299	-0.712	0.113	22	0.155
Sedated	Patroniti 2012	0.298	-0.070	0.667	28	0.113
Sedated	Colombo 2008	0.343	-0.028	0.714	28	0.070
Sedated	Dimussi 2017	0.421	0.023	0.818	25	0.038
Sedated	Terzi 2010	0.983	0.486	1.480	22	0.000
Sedated	Vaschetto 2014	0.837	0.416	1.259	28	0.000
Sedated	Demoule 2017	0.396	0.197	0.595	103	0.000
Sedated		0.413	0.125	0.702	256	0.005
Overall		0.356	0.116	0.596	368	0.004



Groups	Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
	Point estimate	**Standard error**	**Variance**	**Lower limit**	**Upper limit**	**Z-value**	**P-value**	**Q-value**	**df(Q)**	**P-value**	**I^2**	**Tau-squared**	**Standard -error**	**Variance**	**Tau**
Fixed effect analysis															
Non-sedated	0.230	0.097	0.009	0.040	0.421	2.372	0.018	15.107	2	0.001	86.761	0.206	0.247	0.061	0.454
Sedated	0.392	0.065	0.004	0.266	0.520	6.055	0.000	20.862	6	0.002	71.239	0.081	0.071	0.005	0.285
Random effects analysis															
Non-sedated	0.225	0.221	0.049	-0.208	0.659	1.019	0.308								
Sedated	0.413	0.147	0.022	0.125	0.702	2.811	0.005								

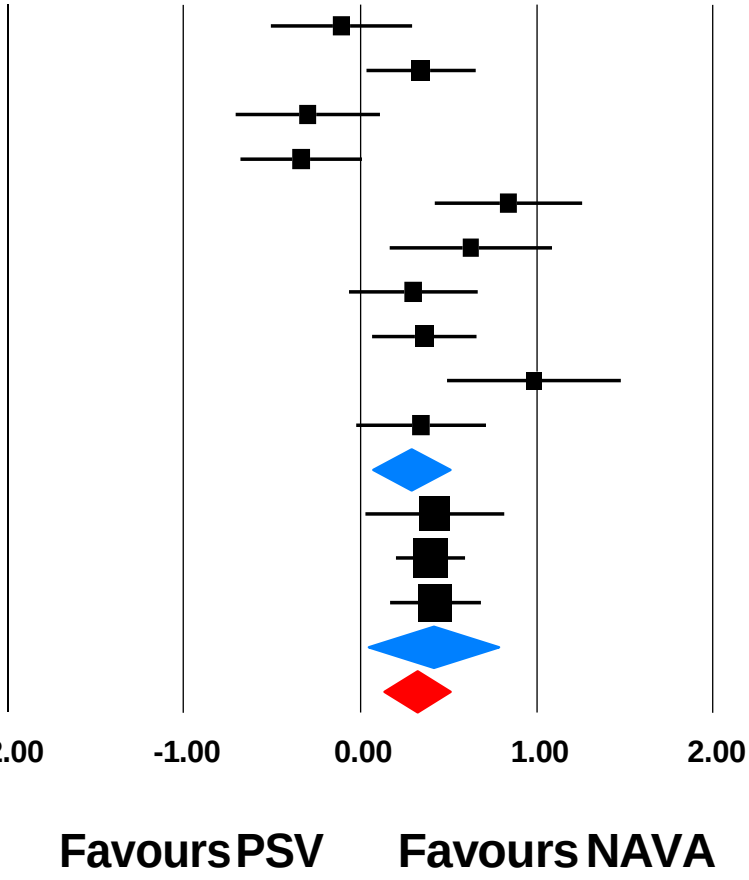
Figure 8: Meta-analysis mixed effects of two RCTs and eight cohort crossover studies depicts the pooled data of an estimated size SMD 0.225, 95% CI: -0.208 -0.659, Z value 1.019, p=0.308, which is a non-statistically significant result of the interventions compared NAVA with PSV in reduction of AI% in a non- sedated group, and an estimated size SMD0.413, 95% CI: 0.125-0.702, Z value 2.881, p=0.005, which is a statistically significant result of the interventions compared NAVA with PSV in reduction of AI% in a sedated group.

An Investigation of clinical differences evaluated the cause of heterogeneity of overall effect size in the AI% by evaluating the effect of sedation on AI% in sedated and non-sedated groups. A random effects meta-analysis in Figure 8 illustrates that in the non-sedated group the estimated summary of effect size, SMD is 0.225 with the Z-value for testing the null hypothesis being 1.019, the 95% CI of -0.208 to 0.659 and associated *p value of* 0.308. It suggests a statistical non-significance difference in effect size. In the sedated group the SMD is 0.413 with the Z-value for testing the null hypothesis being 2.811, the 95% CI of 0.125 to 0.702 and a significance *p* value of 0.05. The Q statistic shows values greater than df in both groups (non-sedated and sedated 15.107>2 and 20.862>6, respectively), and the associated *p* values are significant in both groups (non-sedated is 0.001 and sedated group is 0.002). Both non-sedated and sedated group have a high proportion of I^2 of 86.761% and 71.239%, respectively. T^2 and Tau of non-sedated are 0.206 and 0.454, and T^2 and Tau of sedated group are 0.081 and 0.285.

The information provided by the sedation subgroup analysis to identify which of the subgroups might be homogenous enough to allow an estimate of a combined effect in the subgroup. The summary effect sizes showed that NAVA compared to PSV reduced AI% greater in sedated group than in non-sedated group. The heterogeneity test yielded substantially high proportion of observed variation in effect sizes in both groups, which is not useful for interpreting the combined effect in both groups, so prediction intervals of both groups were calculated. The estimated effect of non-sedated group is 0.225 with the prediction intervals of-6.1917 to 6.6417, and the estimated effect of sedated group is 0.413 with the prediction interval of-0.4110 to 1.2370. Given both prediction intervals, it is expected that in some 95% of all populations, the true effect size will fall in these ranges.

- **Meta-analysis of asynchrony index (%) of randomized controlled trials and cohort crossover studies: Effect of methodological differences / treatment duration on heterogeneity (I^2)**

Group by Treatment duration	Study name	Statistics for each study				
		Hedges's g	Lower limit	Upper limit	p-Value	Total
< an hour	Beloncle 2017	-0.108	-0.512	0.296	0.601	22
< an hour	Ferreira 2017	0.343	0.030	0.656	0.032	40
< an hour	Carteaux 2016	-0.299	-0.712	0.113	0.155	22
< an hour	Schmidt 2015	-0.337	-0.685	0.011	0.058	32
< an hour	Vaschetto 2014	0.837	0.416	1.259	0.000	28
< an hour	Mauri 2013	0.624	0.161	1.088	0.008	20
< an hour	Patroniti 2012	0.298	-0.070	0.667	0.113	28
< an hour	Piquilloud 2011	0.361	0.061	0.661	0.018	44
< an hour	Terzi 2010	0.983	0.486	1.480	0.000	22
< an hour	Colombo 2008	0.343	-0.028	0.714	0.070	28
< an hour		0.287	0.069	0.505	0.010	286
> an hour	Di mussi 2017	0.421	0.023	0.818	0.038	25
> an hour	Demoule 2017	0.396	0.197	0.595	0.000	103
> an hour	Yonis 2015	0.424	0.163	0.686	0.001	60
> an hour		0.413	0.044	0.782	0.028	188
Overall		0.320	0.132	0.508	0.001	474



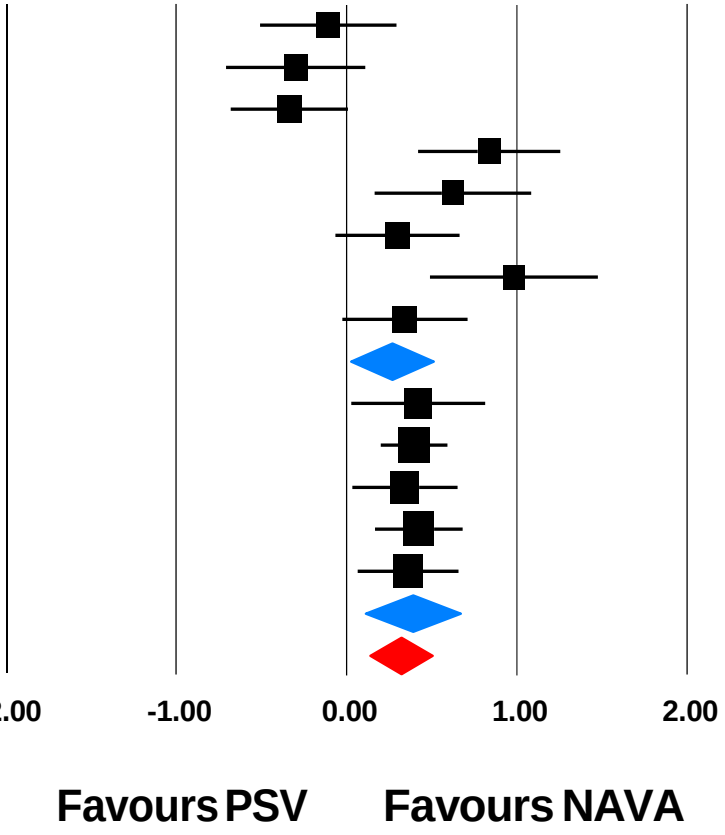
Groups	Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
	Point estimate	**Standard error**	**Variance**	**Lower limit**	**Upper limit**	**Z-value**	**P-value**	**Q-value**	**df(Q)**	**P-value**	**I^2**	**Tau-squared**	**Standard -error**	**Variance**	**Tau**
Fixed effect analysis															
< an hour	0.264	0.061	0.004	0.145	0.383	4.431	0.000	40.208	9	0.000	77.617	0.129	0.080	0.006	0.306
>an hour	0.408	0.075	0.006	0.261	0.556	5.443	0.000	0.033	2	0.984	0.000	0.000	0.019	0.000	0.000
Overall	0.321	0.047	0.002	0.228	0.414	6.798	0.000	42.491	12	0.000	71.759	0.076	0.046	0.002	0.276
Random effects analysis															
< an hour	0.287	0.111	0.012	0.069	0.505	2.557	0.010								
>An hour	0.413	0.188	0.035	0.044	0.782	2.193	0.028								
Overall	0.302	0.096	0.009	0.132	0.508	3.335	0.001								

Figure 9: Meta-analysis mixed effects of two RCTs and 11 cohort crossover studies depicts the pooled data of estimated size SMD 0.287, 95% CI: 0.697 -0.505, Z value 2.557, p=0.010, which is a statistically significant result of the interventions compared NAVA with PSV in reduction of AI% in a more than an hour intervention group, and the pooled data of estimated size SMD 0.413, 95% CI:0.069-0.505, Z value 2.193,p=028, which is a statistically significant result of the interventions compared NAVA with PSV in reduction of AI% in a less than an hour intervention group.

Further investigation of methodological differences to identify heterogeneity was conducted. Figure 9 illustrates graphical and numerical subgroup random effects meta-analysis in two RCTs and 11 crossover studies in a group of the treatments (NAVA and PSV) in optimizing patient ventilator synchrony by measuring the AI%. The treatment group were divided into two groups, which were a less than an hour group and longer than an hour group. The information provided by the treatment-time subgroup analysis to identify subgroup that might be homogenous enough to allow an estimate of a combined effect in the subgroup. The summary effect sizes showed that NAVA compared to PSV reduced AI% greater in > an hour group than in < an hour group. The heterogeneity test yielded I^2 of 0.000% in > an hour treatment group, but not in < an hour group that yielded I^2 of 77.617%. This indicates that NAVA compared with PSV in a > an hour treatment group, NAVA was able to reduce the effect size of AI% nearly a half of SD, and all included study shares a common effect size. However, in a< an hour treatment group, it is not meaningful to interpret the combined effect due to a substantial high proportion of observed variation in effect sizes, so prediction interval was calculated. The estimate effect of < an hour of treatment group is 0.287 with the prediction intervals of -0.5800 to 1.1540 Given the prediction interval, it is expected that in some 95% of all populations, the true effect size will fall in these ranges.

- **Meta-analysis of asynchrony index (%) of randomized controlled trials and cohort crossover studies: Effect of methodological differences/ measurement time on heterogeneity (I^2)**

Group by Measurement time	Study name	Statistics for each study				
		Hedges's g	Lower limit	Upper limit	p-Value	Total
< 20 min	Beloncle 2017	-0.108	-0.512	0.296	0.601	22
< 20 min	Carteaux 2016	-0.299	-0.712	0.113	0.155	22
< 20 min	Schmidt 2015	-0.337	-0.685	0.011	0.058	32
< 20 min	Vaschetto 2014	0.837	0.416	1.259	0.000	28
< 20 min	Mauri 2013	0.624	0.161	1.088	0.008	20
< 20 min	Patroniti 2012	0.298	-0.070	0.667	0.113	28
< 20 min	Terzi 2010	0.983	0.486	1.480	0.000	22
< 20 min	Colombo 2008	0.343	-0.028	0.714	0.070	28
< 20 min		0.267	0.024	0.510	0.031	202
20 min & longer	Di mussi 2017	0.421	0.023	0.818	0.038	25
20 min & longer	Demoule 2017	0.396	0.197	0.595	0.000	103
20 min & longer	Ferreira 2017	0.343	0.030	0.656	0.032	40
20 min & longer	Yonis 2015	0.424	0.163	0.686	0.001	60
20 min & longer	Piquilloud 2011	0.361	0.061	0.661	0.018	44
20 min & longer		0.389	0.109	0.668	0.006	272
Overall		0.319	0.136	0.503	0.001	474



Groups	Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
	Point estimate	**Standard error**	**Variance**	**Lower limit**	**Upper limit**	**Z-value**	**P-value**	**Q-value**	**df(Q)**	**P-value**	**I^2**	**Tau-squared**	**Standard - error**	**Variance**	**Tau**
Fixed effect analysis															
< 20 min	0.225	0.073	0.005	0.083	0.368	3.099	0.002	39.280	7	0.000	82.179	0.196	0.129	0.017	0.443
20 min & longer	0.391	0.062	0.004	0.269	0.512	6.294	0.000	0.217	4	0.995	0.000	0.000	0.014	0.000	0.000
Overall	0.321	0.047	0.002	0.228	0.414	6.798	0.000	42.491	12	0.000	71.759	0.076	0.046	0.002	0.276
Random effects analysis															
<20 min	0.267	0.124	0.015	0.024	0.510	2.155	0.031								
20 min & longer	0.389	0.143	0.020	0.109	0.668	2.726	0.006								
Overall	0.319	0.094	0.009	0.136	0.503	3.414	0.001								

Figure 10: Meta-analysis mixed effects of two RCTs and 11 cohort crossover studies depicts the pooled data of estimated size SMD 0.267, 95% CI: 0.024 -0.510, Z value 2.155, p=0.031, which is a statistically significant result of of the interventions compared NAVA with PSV in reduction of AI% in a < 20 minute measurement time group, and the pooled data of estimated size SMD 0.389, 95% CI:0.109-0.668, Z value 2.726, p=006, which is a statistically significant result of the interventions compared NAVA with PSV in reduction of AI% in a 20 minute and longer measurement time group.

Figure 10 illustrates a graphical and numerical subgroup random effects meta-analysis in two RCTs and 11 cohort crossover studies in a group of duration of measurement (NAVA and PSV) in optimizing patient ventilator synchrony by measuring the AI%. The measurement-time was divided into two groups, which were a less than 20 minute- group and a 20 minute- and longer group. The information provided by the treatment-time subgroup analysis to identify which of the subgroups might be homogenous enough to allow an estimate a combined effect in the subgroup. The summary effect sizes showed that NAVA compared to PSV reduced AI% greater in 20 minute-and longer group than in < 20 minute- group. The heterogeneity test yielded I^2 of 0.00% (20 minutes and longer) and 82.179% (< 20 minutes), which it is not useful to interpret combine effect in both groups, so prediction intervals of < 20-minute group were calculated. The estimate effect of < 20-minute-measurement-time-group is 0.292 with a prediction interval of -0.8580 to 1.3920. Given the prediction interval value, it is expected that in some 95% of all populations, the true effect size will fall in these ranges.

Selection bias analysis

There is one analysis that has been used for bias test in meta-analysis which is a publication bias analysis. It is a form of testing for a selection bias in meta-analysis.[135] A funnel plot is used to display any evidence of publication bias. If there is no publication bias, the funnel plot is shown to have the studies distributed evenly and symmetrically. However, asymmetrical funnel plots can be caused by not only publication bias but also other factors included location biases (English language bias, citation bias, multiple publication bias), true heterogeneity (size of effect differs according to study size), data irregularities (poor methodology design of small studies, inadequate analysis, fraud), artefact (choice of effect measure) and chance.[169] When publication bias occurs, the studies are distributed asymmetrically on the top, not present in the middle and with more missing in the bottom. If the more significant studies are included more than non-significant studies, the studies locate in the top right, middle right and the right bottom with a smaller number of studies located in the left, and no study located in the left bottom. This analysis may provide useful

information; however, it is suggested that this test cannot be used to quantify the effect of publication bias on the overall effect in the meta-analysis.[161]

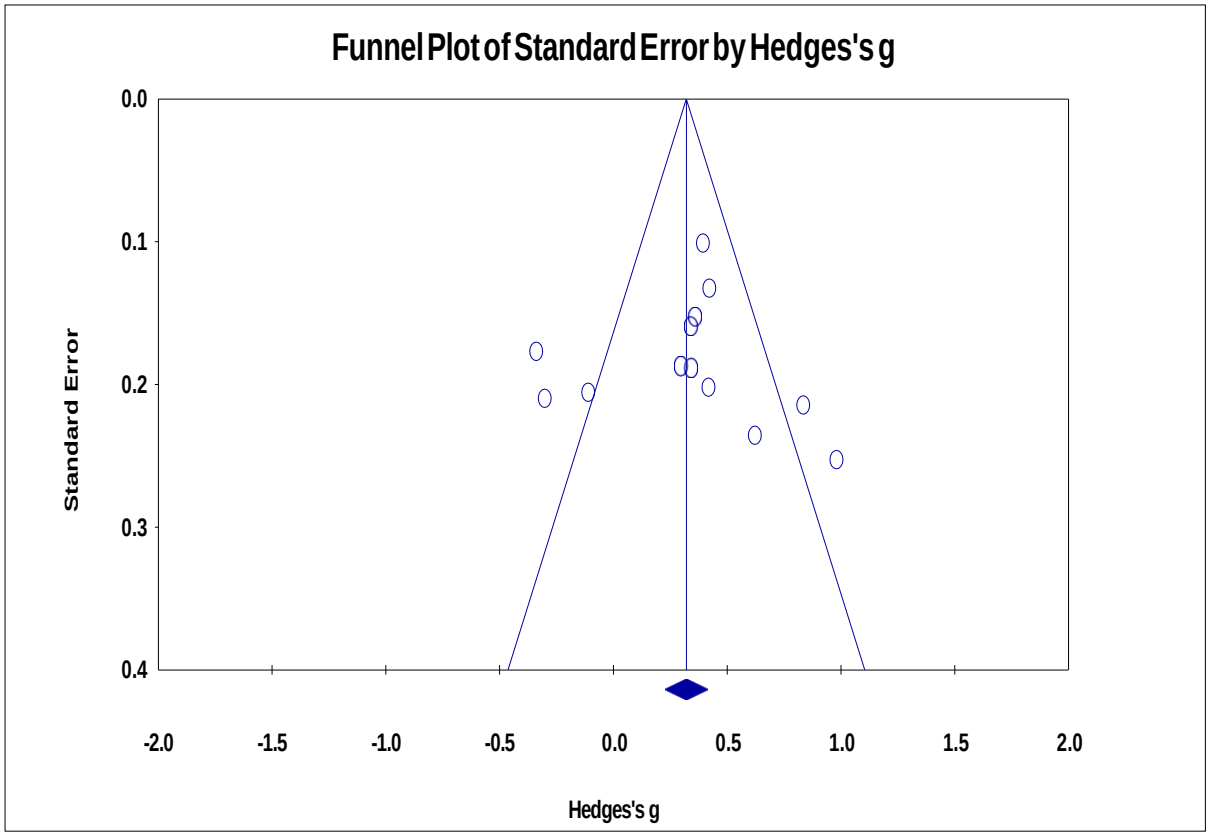


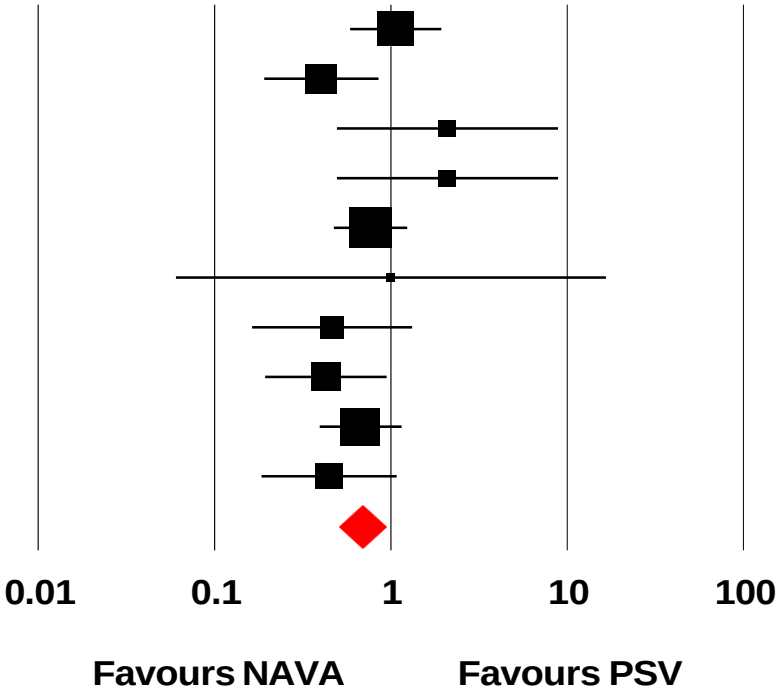
Figure 11: Funnel plot standard error by Hedges's g to assess publication bias of 13 studies comparing NAVA with PSV in reducing AI 10% . A solid vertical line represents a summary estimate of effect size, a diagonal line represents 95% CI.

Figure 11 displays a funnel plot of publication bias analysis in the AI% outcome. There is one study that has the smallest SE on the top and in a significant side, many studies locate close to the line of estimated effect in the middle toward the top. Many studies are missing in the bottom of both sides, one study appears to cross the null hypothesis line (1.0), and more studies appear on the right middle top than the left side. It suggests there are more significant studies that were being published and located than non-significant studies. A visual inspection and subjective impression found the funnel plot shows asymmetry suggestive of bias is likely.

4.6.2. Asynchrony index more than 10%

- **Meta-analysis of asynchrony index >10% of cohort crossover studies**

Study name	CI	Odds ratio	Lower limit	Upper limit	p-Value
Ferreir 2017		1.066	0.584	1.947	0.835
Costa 2017		0.404	0.190	0.858	0.018
Beloncle 2017		2.095	0.491	8.936	0.318
Carteaux 2016		2.095	0.491	8.936	0.318
Yonis 2015		0.766	0.471	1.246	0.283
Schmidt 2015		1.000	0.060	16.684	1.000
Vaschetto 2014		0.464	0.162	1.330	0.153
Patroniti 2012		0.429	0.193	0.954	0.038
Piquilloud 2011		0.674	0.392	1.158	0.153
Colombo 2008		0.446	0.183	1.088	0.076
		0.688	0.514	0.921	0.012



Effect size and 95% confidence interval			Test of null (2-Tail)		Heterogeneity							
Point estimate	**Lower limit**	**Upper limit**	**Z-value**	**P-value**	**Q-value**	**df(Q)**	**P-value**	**I^2**	**Tau-squared**	**Standard - error**	**Variance**	**Tau**
0.688	0.504	0.921	2.513	0.012	11.528	9	0.241	21.929	0.046	0.100	0.010	0.215

Figure 12: Meta-analysis random effects of 10 cohort crossover studies depicts the pooled data of an estimated size OR 0.688, 95% CI: 0.514 -0.921, Z value -2.513, p=0.012, which showed a statistically significant difference in reduction of AI>10% of the interventions compared NAVA with PS

Figure 12 displays a random effects meta-analysis summarized estimated effect size of AI>10%. The analysis is based on 10 cohort crossover studies that evaluated the effect of NAVA compared with PSV in optimizing patient ventilator synchrony by using AI >10% score on partial assist invasive mechanical ventilated critically ill mixed medical and surgical patients in 11 ICUs. These studies were sampled participants from convenience samples of populations assigned to either NAVA or PSV, and the researchers recorded their AI >10% during the treatment duration with measurement time from 5 minutes to 25 minutes. The effect size is the odds ratios. The summary effect size shows it is likely in the clinically important range. The summary effect is OR 0.688 with a 95% CI of 0.514 to 0.921. The I^2 of < 25% is considered a low proportion of heterogeneity. An odds ratio less than 1 is negatively associated with AI> 10%. A shared OR of 0.688 means that AI>10% in NAVA is 31% less likely than in PSV.

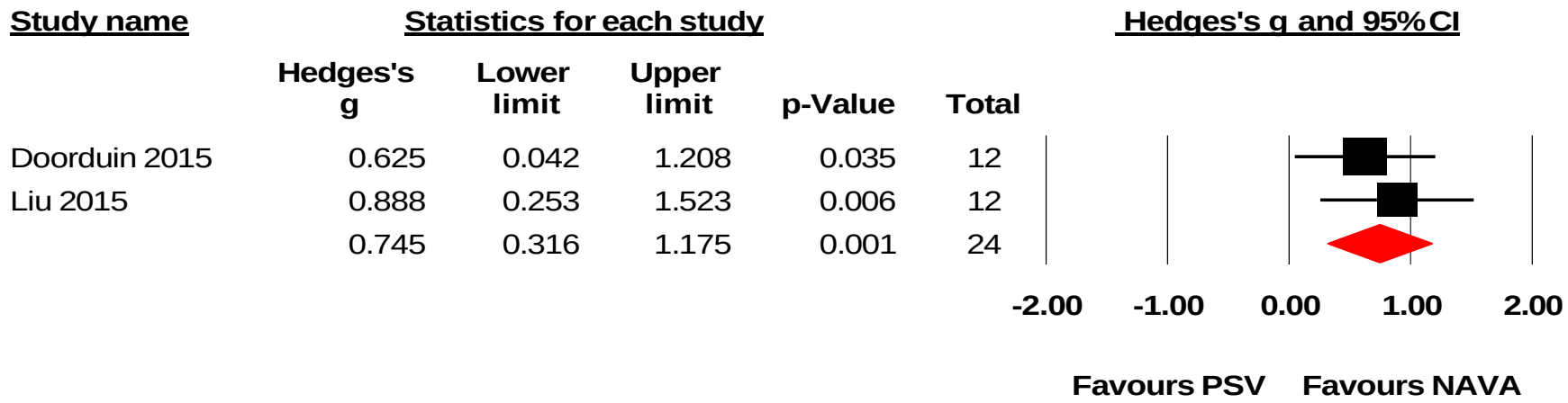
Publication bias analysis

Figure 13 displays a funnel plot of publication bias analysis in the AI>10% outcome. There are more studies appear on the top right than the top left, two largest studies which have the smallest SE locates close to zero on the top of in each side of the summary of treatment effect line and many small studies missing in the middle and lower left than the right side. A distribution of intercept was shifted towards negative value and is very close to -0.5 because the estimated treatment ORs of two largest studies are close to -0.5. The diagonal line shows a very wide 95% CIs. There are also studies missing in the bottom of both sides. It suggests there are more non-significant studies that were being published and located than significant studies. A visual inspection and subjective impression found the funnel plot shows asymmetry. This suggests that bias is likely.

Figure 13: Funnel plot standard error by log odd ratio to assess publication bias of 10 cohort crossover studies comparing NAVA with PSV in reducing AI>10% **. A solid vertical line represents a summary estimate of effect size, a diagonal line represents 95% CI.**

4.6.3. NeuroSync index

- **Meta-analysis of NeuroSync index of cohort crossover trials**



Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity							
Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df(Q)	P-value	I^2	Tau-squared	Standard - error	Variance	Tau
0.745	0.219	0.048	0.316	1.175	3.402	0.001	0.357	1	0.550	0.000	0.000	0.137	0.019	0.000

Figure 14: Meta-analysis fixed effect of two cohort crossover studies depicts the pooled data of an estimated size SMD 0.745, 95% CI: 0.316 -1.175, Z value 3.402, p=0.001, which is a statistically significant difference in reduction of NeuroSync index in the interventions compared NAVA with PSV.

Figure 14 illustrates a fixed effect meta-analysis of effect sizes of NeuroSync index (%) compared between NAVA and PSV. The analysis is based on two studies that evaluated the effect of NAVA in optimizing patient ventilator synchrony by using NeuroSync index on partial assist invasive mechanical ventilated critically ill in COPD and ARDS patients in two ICUs (The Netherlands and China). In each study the patients were recruited from convenience samples that were allocated to NAVA or PSV. The effect size is the SMD. The standardized mean difference is 0.745. On average, patients who were ventilated with NAVA mode had NeuroSync index nearly three quarter of a standard deviation overall effect size lower than those ventilated with PSV mode. The 95% confidence interval of the difference in means is 0.316 to 1.175, which indicates that the mean effect size could fall anywhere between this range, and it does not include an effect size of zero. Furthermore, there is no evidence of a variation true effect. In this case the Q value is 0.357 with 1 df, and *p* value is 0.550. The I^2 is 0.000% indicates that there is no evidence to suggest that there is a portion of the observed variance reflecting differences in the true effect sizes rather than sampling error. As a result, the T^2 and Tau are zero.

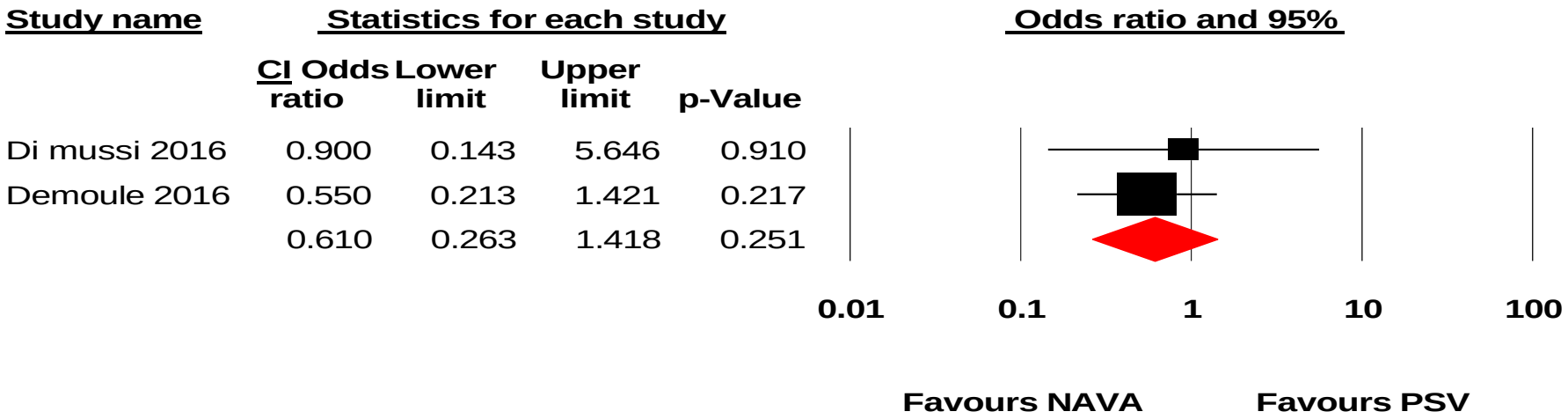
4.6.4. Patient ventilator asynchrony percentage

The patient ventilator asynchrony percentage was reported by one included study. It is a cohort crossover study which evaluated NAVA in a modified Servo 300 ventilator compared to PSV in a group of 14 non-sedated IMV patients who were ready to be weaned from IMV. Twelve of 14 patients had COPD. Patient ventilator interaction was investigated in NAVA and PSV by assessing a trigger delay (an inspiratory trigger delay) and cycling off (expiratory trigger) delay. Other patient ventilator parameters were optimized (see Appendix V). There were two ventilator modes with two factors including PSV -low, which is PSV with the lowest (level of assistance) pressure support patients could tolerate and PSV-high, which is PSV-low with additional of 7 cmH_2O of pressure support, and NAVA with two settings: NAVA-low which was a setting of similar peak airway pressure to the lowest pressure support in PSV mode, and NAVA-high which was a setting of NAVA-low with additional 7 cmH_2O of pressure support. These four ventilator settings were randomly allocated, and the patients were

ventilated on each setting for 10 minutes. The measurement of patient ventilator interaction was recorded for 100 breaths after the 10 minutes of each intervention. The inspiratory trigger delay was measured by the time difference between the onset of Edi and flow, and the cycling off delay was measured by the time difference between the end of neural inspiration and the end of flow inspiratory. Patient ventilator asynchrony percentage was measured by the sum of the trigger delay and cycling of delay per breath and calculated as a percentage of total breath duration.[65] It was found that NAVA in both settings had lower PVA% (7±2%) than PSV-low (18±13%) and PSV-high (23±12%). However, statistical analysis determining the significance was not performed on these outcome datasets by the primary study authors.

4.6.5. Mortality in intensive care unit

- **Meta-analysis of intensive care unit mortality of randomized controlled trials**



Effect size and 95% confidence interval			Test of null (2-Tail)		Heterogeneity							
Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df(Q)	P-value	I²	Tau-squared	Standard - error	Variance	Tau
0.601	0.263	1.418	-1.148	0.251	0.218	1	0.641	0.000	0.000	0.786	0.618	0.000

Figure 15: Meta-analysis fixed effect of two RCTs depicts the pooled data of an estimated size OR 0.610, 95% CI: 0.263 - 1.418, Z value -1.148, p=0.251, which showed a non-statistically significant difference in ICU mortality in the interventions compared NAVA with PSV.

Figure 15 illustrates a fixed effect meta-analysis of the numerical and graphical estimation of overall effect size, observed effects of individual study and heterogeneity in effect sizes of mortality compared between NAVA and PSV. The analysis was based on two studies that evaluated the effect of NAVA compared to PSV on AI% and mortality in critically adult patients with multiple causes of acute respiratory failure in ICUs. Each studies' patients were randomly assigned to either NAVA or PSV, and the researchers recorded the PVD events intermittently during the treatment period of 48 hours. Intensive Care Unit mortality was evaluated via a fixed effects meta-analysis, the odds ratio was 0.610. An odds ratio less than one indicates a negative association with mortality. On average, patients in the NAVA group were likely to have an event (death) 40% less than in the PSV group. The 95% confidence interval for the odd ratios was 0.263 to 1.418. This range includes one (the line of no effect). The result is therefore not statistically significant because the confidence interval includes one. The effect size was small, the number of included studies was small, and the sample size was also too small to demonstrate a significant difference. However, both studies were shown to have a common effect size (Q<df, *p* value of 0.641 and I^2 of 0.00%). In addition, one study also reported a 28-day mortality in patients who were ventilated with NAVA compared with PSV. The authors concluded that the 28 day-mortality rate was not significantly different between NAVA (9%) and PSV 15 %,(*p*= 0.25).[109]

Chapter 5: Discussion

5.1. Summary of findings

This review was conducted to systematically identify available evidence, critically appraise, synthesise and evaluate the effectiveness of NAVA compared to PSV. It is the first systematic review to evaluate effectiveness of NAVA compared to PSV in critically ill invasively mechanical ventilated patients in ICU. Through the analysis of this review, evidence has emerged that there is a gap between current patient ventilator interaction practice and that of optimal patient ventilator interaction practice existing in optimizing patient ventilator synchrony. Many ventilator-setting strategies have been investigated in both ventilator modes to optimize patient ventilator synchrony available in the literature. However, a comprehensive evaluation of the effectiveness of an optimal setting of parameters in each mode, by tailoring to individual patient respiratory demand to optimize patient ventilator synchrony, has not been systematically performed, analysed and synthesised. Based on the results, the setting parameters in each mode that provided the lowest patient ventilator dyssynchrony events were selected for a comprehensive data analysis aimed at comparing NAVA with PSV. These setting parameters were arbitrarily assumed to be optimal in the sense of available data in the literature, but not in the justification from treatment effect size analysis.

To the author's knowledge there is no best available evidence and/or best practice guideline/consensus to optimize patient ventilator interaction/ synchrony by optimally setting ventilator parameters to individual patients with different aetiology of respiratory failure, different lung mechanics and multiple comorbidity in critically ill patients exist. Neural mechanical ventilator sensing is in its early phase of introduction into bedside ICU practice. The evidence of its' use in relation to optimizing patient ventilator synchrony is therefore limited.

The systematic review search conducted in seven electronic databases in 2014 through 2015 when the first systematic review protocol was published, found less than

10 cohort crossover studies. Recently, additional studies were published, which have provided the data to evaluate effectiveness of this intervention. These studies were identified via a comprehensive update search, from five electronic databases, from system email alerts of five databases, and by searching through the references provided from17 studies that met the inclusion criteria. Of these 17 studies, there were two parallel- RCT studies of moderately good quality, and which provided data to evaluate the effectiveness of NAVA compared with PSV in optimizing patient ventilator synchrony.

Influence on patient ventilator synchrony and the evidence of safety

In comparison with PSV, NAVA was strongly associated with reducing of the PVD frequency. This PVD frequency reduction was found in all measurements included reduction of AI% in RCT group and cohort crossover study group, reduction of AI>10% group, NeuroSync index group and PVA% study. However, substantial heterogeneity among study effect estimates of AI% in the cohort crossover studies, sedated and non-sedated group, intervention less than an hour group, measurement less than 20-minute group (75.9%,71.3% 86.8%,77.6% and 82.2%, respectively) indicated that the findings should be interpreted with caution. Although, there were no heterogeneity found in the RCTs group, treatment longer than an hour group, and measurement 20 minute and longer group, and a small proportion of heterogeneity found in AI>10% group (21.9%), these findings were from only two RCTs (measured AI%), 13 studies (two RCTs and 11 cohort crossover studies) in treatment longer than an hour and measurement time 20 minute and longer groups that measured AI%. In the AI>10% group the summary of effect size was from 10 cohort crossover studies with moderate to high quality of evidence and high risk of bias.

With substantial reduction of NeuroSync index and no heterogeneity found in the NeuroSync index group, the summary effect was from only two cohort crossover studies with a small number of participants. Similarly, the PVA% effect was analysed from only one cohort crossover study.

Influence on mortality

Neurally adjusted ventilatory assist did not show a significance difference in reduction of the ICU mortality when compared with PSV. This effect was estimated from two RCTs with moderate to large sample size and no heterogeneity. A twenty-eight-day mortality which reported by one study found to have no significance difference.

In conclusion, neurally adjusted ventilator assist is considered to be safe to use as in part it reduced the PVD frequency. However, there were only two RCTs with a total sample size of 153 patients that provided evaluation of effectiveness and safety (AI% and mortality). Neurally adjusted ventilatory assist showed a weak association with reducing of mortality compared with PSV. In addition, an assessment of publication bias found the evidence of asymmetrical funnel plots in AI% and AI>10% outcomes. These findings suggest that publication bias is likely therefore; an interpretation of our meta-analysis outcomes should be caution and cannot prove the apparent outcomes are due to bias.

5.2. Limitations of the systematic review

Overall the quality of the evidence was considered moderate in a crossover study to moderate to high in RCT studies and the majority of studies were rated as having a high risk of bias across six domains of bias (random sequence, allocation concealment, incomplete outcome data, selective reporting, blinding of participants and investigator and blinding of outcome assessor). Given characteristics of the intervention, the clinicians cannot be blinded to the intervention due to the nature of the treatment, as it is not feasible to conduct the treatment without possibly being aware of the ventilator settings.

Most of the included studies are a cohort crossover study (15 trials). This study design causes a concern of some biases toward a treatment effect. Based on the reviewers' assumption, in those studies the study investigators took all reasonable considerations

and actions to minimize the effect of study design. The factors that can cause concern are a time period effect, a time period by treatment interaction, a carryover, patient by treatment interaction, and patient by time period interaction. These factors might cause the crossover differences not to be distributed at random about true treatment effects.[170] As a minimum, the first factor (period effect) and third factors (carry over) are considered. Considering the two factors, randomization must be applied, and with carryover effects, the investigator must design the study to have a wash out period that is adequate to eliminate the effect of the previously given treatment.[170] In the clinical study of NAVA compared to PSV, only an active wash out is clinically possible and ethically acceptable, as well as limited measurement outcomes must be measured in the latter part of the study period to minimize the risk of a carry-over effect. When multiple interventions are being investigated, a consideration of the length of time a treatment takes to reach a steady state; the wash out period for the trial must be no less than the longest presumed time to reach steady state for any treatment to prevent a carryover effect. To the authors knowledge, what is believed to be the best knowledge and scientific evidence available to time to support the wash out period used in the trial was sufficient to eliminate the effect of a treatment given previously is probably a study by Viale et al 1998. This study assessed time course evolution of ventilatory responses to inspiratory unloading when adjusting the pressure support in PSV. The ventilator settings were altered by changing Paw, the Pes swing and integrated electro-myo-diaphragmatic activity (∫EMGdi), the duration required to achieve stabilization was about six to eight breaths.[136]

To possibly minimize the potential bias in the review process, the systematic review process outline by the JBI Reviewers' Manual was followed, and the librarian was consulted for a systematic search for evidence. The critical appraisal process was conducted by two authors (AP and DC), and any disagreement between both authors was discussed with the third author (CL). Study selection (exclusion and inclusion) was performed by all three authors. The data extraction, synthesis and analysis were performed by the primary author. The outcome data were available for approximately 90% of participant (n=398), of which there were 86.7% for asynchrony index (AI) %, 95.38% for AI>10%, 100% for NeuroSync index, 100% for patient ventilator

asynchrony (PVA)% and 92.2% for ICU mortality. Even though literature searches were conducted rigorously and an alert system from the electronic databases were set up, we could never be certain that we have included all studies that meet inclusion criteria. In addition, searches conducted were limited to find English only publications, which possibly eliminated the chance of finding studies published in other languages. To identify and evaluate the risk of publication bias a funnel plot was used and presented. It showed asymmetrical funnel plots for both AI% and AI>10%, which suggests bias is likely, and the extent of this bias affects the summary outcomes is uncertain.

5.3. Implications for practice

Based on the data from 17 studies with a total of 398 participants who provided 729 datasets for analysing the effectiveness of NAVA compared to PSV, utilization of NAVA with optimal setting parameters (ITS, ETS, PEEPe, V_T and PS) tailored to patient respiratory demands is able to reduce patient ventilator dyssynchrony events (AI%, AI>10%,NeuroSync index and PVA%). The reduction of the AI% is more likely to be notable in groups where patients were sedated, had the treatment > an hour group and measurement of PVD event 20 minutes or longer. The identified reduction of AI>10% in NAVA group compared with PSV group is unlikely to be clinically and practically meaningful because of a lack of a high-quality evidence of AI>10% studies that investigated the effects of AI>10% on patient clinical important outcomes. Therefore, this finding is of limited patient benefit. The meta-analysis of data in ICU mortality and the NeuroSync index demonstrate preliminary outcomes in any evaluation of the effectiveness of NAVA compared with PSV in these study populations, and it is not generalizable to other groups of a population. Furthermore, a PVA% study report can provide insightful knowledge into patient ventilator interaction with these two modes; this can be of less justifiable benefit in possible outcomes.

Optimizing patient ventilator interaction is an emerging outcome objective that clinicians practicing in the field have recently gained interest in. Since the neural sensor (Edi catheter) with NAVA was introduced in ICUs, there have been more

studies conducted to evaluate its effectiveness in reducing patient ventilator dyssynchrony, and other important patient outcomes such as mortality, length of ICU stay and length of IMV use. However, the number of completed and published studies of NAVA as compared with PSV was limited and was further compounded by a moderate quality of studies in crossover studies, a moderate to high quality in RCTs and a small number of participants. It can be stated that the available evidence that was used to synthesise and analyse the effectiveness of NAVA compared to PSV is insufficient to provide a statistical meaningful recommendation. However, it is able to provide an insight into current clinical practice related to optimizing patient ventilator synchrony.

5.4. Implications for research

Given the outcome report from a statistical analysis of individual study's effect size and the heterogeneity test, which provides a high proportion of heterogeneity in a crossover study group that investigated the AI%, and in its' subgroup analysis in a group of sedated, non-sedated, shorter duration (< an hour) and shorter measurement time (< 20 minutes)), there is a need for a specifically tailored and appropriate study designs; ideally, adequately powered, high quality and multi centre randomized controlled trials among this group of patients. This will investigate the effects of NAVA in patients' surrogate outcomes (AI%, AI>10% and NeuroSync index) when compared with PSV, and, further, evaluate an association/ effects of these patient's surrogate outcomes on patient's important outcomes i.e. mortality, ICU length of stay, and duration of IMV. This study trial will have ventilator parameter setting strategies that optimize patient ventilator synchrony in both intervention mode and comparator mode for each individual patient. Such settings will include ITS to prevent auto trigger, and ETS to match appropriate patient respiratory cycling off time and prevent unintentional creation of an intrinsic PEEP and optimal PEEPe to optimize patient ventilator synchrony. The levels of assistance in each mode (PS in PSV and NAVA gain in NAVA) need to be adjusted appropriately to the setting of V_T and Paw. Furthermore, given sedative agents to some patients to optimize patient ventilator interaction if required, is recommended. Essentially, the treatment duration and measurement time

need to be conducted as long as possible to be sufficient in justifying the outcome difference. Ideally, a continuous monitoring PVD event during the whole duration of the trial must be carried out.

In summary, it is recommended that the study should have the following PICOs and practices:

1. Participants should be as homogenous as possible to represent the population of interest that is critically ill patients who are intubated and ventilated (meeting a standardised weaning criteria) in the period of weaning trial with an appropriate weaning strategy (weaning protocol).
2. Intervention and measurement of AI% should be carried out in a justifiable time frame according to the outcomes; i.e. a whole period of intervention if the mortality outcome was measured. The intervention of NAVA should have NAVA settings to minimize PVD frequency, the settings should be appropriate justified from a high level of evidence. The settings to minimize PVD frequency in NAVA must include at least ITS, ETS, PEEPe and NAVA gain. The identical level of assistance between NAVA and PSV have to identify and report in each individual patient, this could be done by using V_T, Paw, Edi level or work of breathing parameter to justify the level of support.
3. Pressure support ventilation as a comparator needs to be appropriately set to minimize the PVD frequency, the setting parameters are ITS, ETS, PEEPe and PS level.
4. Outcomes of PVD frequency should be done continuously until the end of the study period. The effective and reliable measurement tool and method should be used for outcome measurement i.e. continuous monitoring and real-time analysing of PVD frequency. Appropriate justification and computed data should be used if there is an attrition.
5. To improve the methodological quality in conducting a primary study, it is recommended to conduct the research to reduce/ eliminate six domains of bias.
6. To provide a transparent report of the trial, the guideline for reporting a parallel RCT in the CONSORT statement is recommended.[171]

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APPENDICES

Appendix I: Systematic review protocol

Effectiveness and safety of Neurally Adjusted Ventilatory Assist (NAVA) mechanical ventilation compared to standard conventional mechanical ventilation in optimizing patient-ventilator synchrony in critically ill patients: a systematic review protocol

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Review question/objective

The objective of this systematic review is to systemically identify, appraise and synthesize the best available evidence regarding the safety and effectiveness of invasive mechanical ventilation (IMV), in optimizing patient-ventilator interaction by using the Neurally Adjusted Ventilatory Assist (NAVA) compared with Pressure support ventilation (PSV) in critically ill adult patients in intensive care units (ICUs). The specific questions this review sought to address were:

Does NAVA influence patient-ventilator dyssynchrony measured by using asynchrony index (AI), NeuroSync index and patient ventilator asynchrony percentage compared to conventional mechanical ventilation among critically ill adult patients on invasive mechanical ventilation (IMV) support in an intensive care environment?

What is the evidence of safety related to use of NAVA compared with PSV among critically ill adult patients in an intensive care environment?

Background

Invasive mechanical ventilation is a common intervention in ICUs. It is used to sustain respiratory function in acute respiratory failure when a patient's ventilatory capabilities are unable to adequately meet the metabolic demands of the body.[1,2] The goals of mechanical ventilation are to reduce excessive respiratory effort, ensure adequate oxygenation,[3] avoid ventilator induced lung injury, and optimize patient-

ventilator synchrony.[4-6] Patient-ventilator asynchrony (PVD) occurs frequently in ICUs. Numerous investigators have reported a number of asynchrony incidences. It ranges from 10-88% of breathing observations during assisted mechanical ventilation.[7-14] Patient-ventilator asynchrony may occur as a result of inadequate or excessive sedation[15] and suboptimal ventilator settings,[16-20] and it is associated with adverse clinical consequences including hypoxia, cardiovascular compromise, anxiety and fear,[21] patient discomfort,[14,17,22-24] sleep fragmentation,[25,26] prolonged mechanical ventilation,[14] and possible diaphragmatic injury.[27-29] It is also associated with a longer duration of mechanical ventilation, longer ICU stay, and increased morbidity[10] and mortality.[4] Therefore, identifying the best modality of IMV to optimize patient-ventilator interaction is a necessary empirical goal in minimizing adverse outcomes and providing optimal care to ventilated critically ill patients.

Internationally, epidemiology of IMV in adult ICUs from an analysis of the Simplified Acute Physiological Score III (SAPS III) Project database demonstrates that 53% of intensive care patients are mechanically ventilated.[30] The rates of IMV have increased more than 10% over a seven-year period,[31] contributing to a substantial increase (approximately 44%) in the annual critical care cost and accounting for 13% of total hospital costs.[32] Additionally, intensive care costs for mechanically ventilated patients is more than US$2000 per day.[33]

Mechanical ventilation can be used to support a patient's ventilatory system by delivering breaths, which can be either controlled or assisted.[3 34,35] It can be set to control airway pressure, flow, volume and respiratory timing or a combination of them and to synchronize with the patient's neural breathing efforts (neural trigger) and inspiratory effort.[36] In synchronizing with the patient's inspiratory effort It works also either by the reversal of the expiratory flow (flow sensor) or by a drop in the pressure (pressure sensor). These mechanisms are known as a pneumatic trigger.[37]

Patient-ventilator dyssynchrony can be defined as a mismatch between the patient and ventilator inspiratory and expiratory times.[29,38,39] It is also referred to as the difficulty of harmonizing the respiratory cycle generated by the complex respiratory control system with the mechanical cycle of the ventilator,[40] and the uncoupling of the mechanical delivered breath (ventilator) and the neural respiratory effort (patient). Patient-ventilator asynchrony can be detected by measurement of electrical activity of respiratory muscles (diaphragm or transverse abdominus) or esophageal pressure[38,41] or ventilator graphic waveforms.[14,18] Patient-ventilator asynchrony is associated with the conventional assist modes, which are influenced by multi-factors related to both ventilator and patient[21,42,43] Patient-related factors of asynchrony include respiratory mechanics, minute ventilation, respiratory muscle capacity, and respiratory drive. Ventilator factors include the method of respiratory triggering, i.e. pneumatic trigger and neural trigger. Furthermore, the interface of the ventilator circuitry and humidification system can contribute to PVA.[9,17]

Triggering asynchrony is found to be only one type of problem associated with suboptimal patient- ventilator interaction.[18] Asynchrony events are more frequent with pneumatic triggered compared to neural triggered IMV.[44-48] Unsuccessful weaning in prolonged weaning patients is associated with a high incidence of ineffective triggering.[8] Muscle fiber injury and diaphragm injury and atrophy are caused by excessive assistance and prolonged support from mechanical ventilation.[8,49-51] Conventional ventilation can induce loss of inspiratory muscle force, as much as 75%.[52,53] An asynchrony index at least 10% contributes to a longer

duration of mechanical ventilation as well as a higher rate of tracheostomy in medical patients.[14] However, it is not associated with prolonged IMV in trauma patients.[13] Ventilator asynchronized patients tend to receive excessive levels of ventilator support,[14] and sedation.[10] Additionally, adjusting the pressure support level[54] and the sedation level can alter PVD.[11] Furthermore, there has been a report that 42% of all increases of sedation account for PVD.[55] Conversely, greater sedation is associated with increased risk of ineffective effort[11] Therefore, reduced duration of mechanical ventilation, promoted spontaneous breathing,[13,56-60] and reduced sedation are factors that contribute to positive outcomes in mechanical ventilated patients[61-66] that may be caused by optimizing patient-ventilator interaction.

An ideal approach in optimizing patient-ventilator interaction would be to connect the patient respiratory centers to the ventilator, as similarly and naturally as the brain stem is connected to the respiratory muscles via the phrenic nerves.[3] The technique of transforming neural drive into ventilator support output is by measuring of the neural excitation of the diaphragm, which is a diaphragmatic electrical activity (Edi). The diaphragmatic electrical activity signal is then used to control NAVA. The diaphragmatic electrical activity is generated by the neural respiratory output signal from the brain stem, and is modulated by input from multiple respiratory reflexes feedback to the respiratory centers.[36]

Recently, advances in computer technology have made it possible to obtain reliably diaphragmatic electrical activity, free of artifacts and noise and in real time.[67,68] A new modality of neurally trigger ventilator was introduced to a clinical practice to improve patient-ventilator synchrony.[34] A neurally trigger mechanical ventilation is called *Neurally Adjusted Ventilatory Assist (NAVA)*,[36] the latest development of mechanical ventilation that became available to clinicians in a clinical setting. Neurally Adjusted Ventilatory Assist may be considered to be an assist mode where the level of ventilatory assist is proportional to diaphragm muscle electrical activity. The timing and intensity of the Edi signal both determine the timing and intensity of the ventilatory assist, resulting in a high level of synchrony.[37] The diaphragmatic electrical activity signal reliably monitors and controls the ventilatory assist.[69]

Neurally Adjusted Ventilatory Assist uses Edi to trigger and cycle off the ventilatory assist and to control the inspiratory ventilation.[70] The diaphragmatic electrical activity is obtained from the crural portion of the diaphragm via a nasogastric feeding tube with an array of eight bipolar electrodes mounted at its distal end. The signals are amplified, band-pass filtered and digitized.[71] With NAVA, the ventilators apply pressure to the airway opening throughout inspiration in proportion to the Edi signal times. A preset gain constant is referred to as the NAVA level. Therefore, during inspiration, peak airway pressure (Paw) is instantaneously coupled to Edi. The support delivery is under the patient's control. This corresponds to patient demands, irrespective of variations in muscle length or contractility.[72]

Several studies have evaluated the impact of increasing pressure support levels versus NAVA levels, using similar methods of setting the ventilator. All studies show that NAVA averts the risk of over assistance when the assist level increased gradually. In addition, NAVA does not depend on measurement of airway pressure or flow, and is synchronous with inspiratory (neural) efforts, which is independent of the presence of leaks or intrinsic positive end expiratory pressure (PEEPi), therefore, brings about improved patient-ventilator synchrony.[9,73-78] In contrast, there has been a report that a very high level of NAVA results in unstable periodic breathing patterns

with delivery of high tidal volume, followed by periods of apnea and signs of discomfort.[79]

Based on original physiological concepts, NAVA adds a new modality to patient-ventilator interaction during spontaneous breathing by using Edi. There is compelling evidence that NAVA improves patient-ventilator interactions and increases respiratory variability in comparison with conventional pneumatic triggering ventilators, which have a number of limitations in correcting the inappropriate timing and delivering of pressure.[9,80,81] Many investigators have conducted numerous clinical trials to evaluate the safety and efficacy of NAVA, since it was first introduced into clinical practice. There is clear evidence that NAVA is safe and effective in optimizing patient-ventilator synchrony compared to the conventional mechanical ventilation modalities.[9,41,73,75,76,82] Several clinical trials (ongoing studies) have been registered to evaluate a newly advanced neural trigger ventilation modality.[83] However, to date there is no systematic review available to inform and guide clinicians in the clinical setting regarding safety and effectiveness of NAVA. Therefore, a systematic review to analyze and synthesize the best available scientific evidence is proposed to measure outcomes across included studies regarding the safety and effectiveness of NAVA as a solution to inefficient patient-ventilator interactions. This systematic review protocol is a revised version of the previous published protocol.[84] It was modified for appropriateness in relation to meet the requirement of a Master of Clinical Science degree, availability of scientific evidences and to provide a meaningful evidence to support evidence-based policy and practice.

Keywords

patient-ventilator interaction; patient-ventilator dyssynchrony; Neurally Adjusted Ventilatory Assist; invasive mechanical ventilation

Inclusion criteria

Types of participants

This review will consider critically ill adult patients across all demographic groups, with or without existing comorbidities, and with any causes precipitating respiratory failure requiring IMV via endotracheal intubation and tracheostomized intubation in intensive care units.

Types of intervention

This review will consider studies that evaluate the safety and effectiveness of NAVA by measuring asynchrony index percentage (AI%). The primary intervention of interest was NAVA with an optimal ventilatory support setting. If multiple levels of NAVA gain factor (level of assistance) were studied, they are defined as potentially suboptimal (low assistance), optimal (adequate assistance) and high (over assistance). The optimal setting of NAVA (examined by the authors and as stated by the primary study authors) were considered and synthesized. The study that used only one group of setting parameter of NAVA and standard setting of PSV are considered optimal setting in this regard.

Types of comparators

This review will consider the studies that used PSV as comparators for the intervention. Pressure support ventilator with different levels of pressure support assistance, levels of ITS, levels of ETS and level PEEPe can be defined as suboptimal (low-assistance), adequate (optimal-assistance) and high (over-assistance). The optimal level is the level that showed to have the lowest PVD events (AI%) or NeuroSync index or patient ventilator asynchrony percentage (PVA%), or the primary study authors stated that it is the optimal setting. The optimal setting levels are classified based on available scientific evidence in the literature according to the primary investigator's report data, and it is an arbitrary level.

Types of outcomes

This review will consider studies that include the following outcome measures:

1. Frequency of PVD: It can be measured by using electrical activity of diaphragmatic graphic waveform and/ or esophageal pressure graphic waveform compared to ventilator graphic waveform (flow or pressure wave form). Dyssynchony can be calculated by either using asynchrony index (AI) or NeuroSync index or patient ventilator asynchrony percentage. Asynchrony index (express as percentage) is calculated by (number of asynchrony events ÷ total respiratory rate + ineffective effort) x 100.[14] NeuroSync index is measured by a validated automated computer algorithm that reports timing errors between Paw and Edi,[80,81] and PVA% is defined as the sum of triggering delay and cycling off delay per breath which expressed as a percentage of the total breath duration.[76]

2. Mortality from all causes and from IMV related. Analysis of mortality affected by using NAVA and PSV which measured AI% in only included parallel study design will be performed.

Types of studies

This review will look at any experimental study design, including randomized controlled trials, non- randomized controlled trials and quasi-experimental studies. Additionally, in the absence of experimental studies, the observational study designs including; prospective and retrospective cohort studies and case control studies, will also be included.

Search strategy

The search strategy aims to find published studies. A three-step search strategy will be utilized in this review. Firstly, an initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract and of the index terms used to describe the article. Secondly, search using all identified keywords and index terms will then be undertaken across all included databases. Finally, the bibliographies of retrieved trials, in progress trials and review papers will be searched for potential relevant trials. Studies published only in English will be considered for inclusion in this review. In addition, the first authors of relevant included studies will be contacted to obtain further information if required.

Electronic databases to be searched (from 2007 when the first human trials were conducted)[85] include:

MEDLINE (PubMed)

EMBASE

Cochrane

Cochrane Central Register of Control Trials

Web of Science

www.ClinicalTrials.gov

The initial key words will include: "Neurally Adjusted Ventilatory Assist", "NAVA", "pressure support ventilation", "volume-controlled ventilation", "pressure-controlled ventilation", "artificial respiration", "invasive mechanical ventilation", "asynchrony", "dyssynchrony", "patient-ventilator interaction", patient-ventilator asynchrony" All search terms will be combined using Boolean operator OR and AND.

Assessment of methodological quality

Selected studies for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review. Standardized critical appraisal instruments for use in systematic reviews from the Joanna Briggs will be used.[86] Appendix I shows of critical appraisal tools. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from study papers included in the review using the standardized data extraction tool from JBI-MAStARI in paper format (Appendix II).[87] The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Data from papers, where possible, will be pooled in statistical meta-analysis using the Comprehensive Meta-Analysis (CMA) software.[88] All results will be subjected to double data entry to minimize the risk of error during the data entry. Where appropriate, Relative Risks and/or Odds Ratios and their associated 95% confidence interval will be calculated for analysis of categorical data. For continuous data collected using the same scale, the weighted mean differences (WMD) and standard deviation will be calculated. For data collected using different scales, the standardized mean differences (SMD) will be calculated. Statistical heterogeneity will be assessed using standard Chi square test and if found will be investigated prior to any further analysis. Where appropriate, a meta-analysis will be conducted using CMA software. Where statistical pooling is not possible, the findings will be presented in narrative form.

Conflicts of interest

None of the authors have conflicts of interest.

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Appendix II: Search strategy

PubMed Search

A complete search strategy for MEDLINE by searching PubMed interface

A search strategy is based on the main concepts being examined in the review. These concepts included the keywords in the title, eligibility criteria for studies to be included; they were used to assist in the selection of appropriate subject headings and text words for the search strategy.
All relevant keywords and text words were searched in each database interface to find controlled vocabularies and text words or thesauruses that are a standardized subject term assigned by indexers. A logic grid for each database was formulated into a table, and then each individual search term was used to search in each search interface accordingly.
Following is a step for comprehensive searching in each database:

1. The keywords that relevant to the systematic review concepts and PICO were identified.
2. Each keyword was used to find controlled vocabularies or text words or thesauruses which is a standardized subject term (indexing term) assigned by indexers in each database interface.
3. The standardized subject terms for individual database were built with synonyms, related terms, variant spellings, truncation and wildcards then formulated into a table for each database as an individual database logic grid.
4. Each standardized subject term in each logic grid column then used to test for sensitivity and precision at a time.
5. Each individual search results (item found) then joined with BOOLEAN operators AND, OR and NOT within each column, then within between column.
6. Each individual item found then scan reading to identify sensitivity and precision.
7. The final search was based on the most sensitivity; precision and relevant to concepts of review, standardized subject terms that found the most relevant terms.
8. The final item founds (search results) from each database then exported into a bibliographic software or reference management software, EndNote.
9. Duplicate items were identified and removed by using EndNote function.

Comprehensive searching for PubMed

1. Step 1: Identified keywords, which relevant to the systematic review concepts and PICO. Including Neurally Adjusted Ventilatory Assist, mechanical ventilation, asynchrony, dyssynchrony, synchrony, and patient ventilator interaction.
2. Step 2: Indexing terms in PubMed were searched in Mesh database. Items were found as following:

- Neurally Adjusted Ventilatory Assist is “Interactive Ventilatory Support” [Mesh] which indexed in 2012.
- Mechanical ventilation which indexed as “Respiration, Artificial” [Mesh]
- Asynchrony, dyssynchrony, synchrony, and patient ventilator interaction none of the terms were found indexing in the PubMed, so the following term truncation asterisk (*) and PubMed syntax [tw] were used in order to find the most relevant studies.

3. Step 3: The standardized subject terms then formulated into a table for the PubMed logic grid as shown below.
4. Step 4: Each standardized subject term in each logic grid column then used to test for sensitivity and precision at a time. No filter and limit were used.
5. Step 4 to step 7 explicit as following:
6. The final item founds (search results in the table of results i.e. #32) from each database then exported into a bibliographic software or reference management software, EndNote.

A		**C**
"Interactive Ventilatory Support"[Mesh] OR Neurally Adjusted Ventilatory Assist*[tw] OR Neural trigger*[tw] OR NAVA [tw] OR Neurally Adjusted Ventilatory AssistNEXT20 (NAVA) OR Neurally adjusted ventilatory assist	Respiration, Artificial [Mesh] OR Artificial Respirat*[tw] OR Ventilation, Mechanical*[tw] OR Mechanical Ventilat*[tw]	Asynchron*[tw] OR dyssynchron*[tw] OR Dysynchron*[tw] OR Synchron*[tw] OR Patient-ventilator interact*[tw] OR Patient-ventilator asynchrony*[tw] OR PVA [tw]

Following is a table of search outcomes from PubMed search on 30th of March 2018.

Search	Add to builder	Query	Items found
#15	Add	Search **(#1) OR #2** Filters: **Clinical Trial**	59
#16	Add	Search **(#1) OR #2** Filters: **Clinical Trial; Humans**	58
#14	Add	Select **382** document(s)	382
#13	Add	Search **(#1) OR #2**	382
#12	Add	Search **((#1) AND #2) OR #4**	109649
#11	Add	Search **((#1) OR #2) AND #4**	155
#10	Add	Search **((#1) OR #2) OR #4**	109698
#9	Add	Search **((#1) AND #2) AND #4**	152
#8	Add	Search **(((#1) AND #2) AND #3) AND #4**	144
#7	Add	Search **((#1) AND #2) AND #3**	294
#6	Add	Search **(#1) AND #2**	330
#5	Add	Search **(((#1) OR #2) OR #3) OR #4**	206903
#4	Add	Search **(Asynchron*[tw] OR dyssynchron*[tw] OR Dysynchron*[tw] OR Synchron*[tw] OR Patient-ventilator interact*[tw] OR Patient-ventilator asynchrony*[tw] OR PVA[tw])**	109471
#3	Add	Search **(Respiration, Artificial [Mesh] OR Artificial Respirat*[tw] OR Ventilation, Mechanical*[tw] OR Mechanical Ventilat*[tw])**	98899
#2	Add	Search **("Interactive Ventilatory Support"[Mesh] OR Neurally Adjusted Ventilatory Assist*[tw] OR Neural trigger*[tw] OR NAVA[tw] OR Neurally Adjusted Ventilatory AssistNEXT20 (NAVA) OR Neurally adjusted ventilatory assist)**	382
#1	Add	Search **Neurally adjusted ventilatory assist**	330

Table 1: Outcomes from updated search

Databases and Search Conducting Date	Controlled vocabulary and indexed terms used in search interfaces	Boolean operator used	Filters and limits	Item(s) found
Cochrane (CENTRAL) 30.03.2018	"Neurally Adjusted Ventilatory Assist"	None	Trial	95
EMBASE 06.04.2018	'neurally adjusted ventilatory assist'/exp OR 'neural trigger*' OR 'interactive ventilatory support'/exp	OR	No limit or filter	285
MEDLINE (PubMed) 30.03.2018	(neurally adjusted ventilatory assist) OR ("Interactive Ventilatory Support"[Mesh] OR neurally adjusted ventilator Assist*[tw] OR neural trigger*[tw] OR NAVA [tw] OR neurally adjusted Ventilator assistnext20 (nava) OR neurally adjusted ventilatory assist)	OR	No limit/ filter	382
SCOPUS 30.03.2018	(TITLE-ABS-KEY ("Neurally adjusted ventilatory assist") OR TITLE-ABS-KEY ("Interactive Ventilatory Support") OR TITLE-ABS-KEY ("Neural trigger*")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "NEUR") OR LIMIT-TO (SUBJAREA , "ENGI")) AND (LIMI T TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (LANGUAGE," English")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT TO (ACCESSTYPE (OA)) OR LIMIT TO (ACCESSTYPE(OTHER)))	OR and AND	Date 2007 to Present (30.03.2018), subject area, humans, English journal, humans, journal, access type (open and others)	280

Databases and Search Conducting Date	Controlled vocabulary and indexed terms used in search interfaces	Boolean operator used	Filters and limits	Item(s) found
www.ClinicalTrials.gov 30.03.2018	Neurally adjusted ventilatory assist | Completed Studies | Adult, Senior	None	Completed studies, adult and senior	35
Additional Resources Electronic database alert from each database and study reference reading	As per each database indexed terms	As per each database used	As per each database used	1

Appendix III: Joanna Briggs Institute (JBI) Critical Appraisal Instruments

THE JOANNA BRIGGS INSTITUTE

The Joanna Briggs Institute

Introduction

The Joanna Briggs Institute (JBI) is an international, membership based research and development organization within the Faculty of Health Sciences at the University of Adelaide. The Institute specializes in promoting and supporting evidence-based healthcare by providing access to resources for professionals in nursing, midwifery, medicine, and allied health. With over 80 collaborating centres and entities, servicing over 90 countries, the Institute is a recognized global leader in evidence-based healthcare.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available literature (that is, evidence) and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. The JBI takes a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, the Institute has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. There now exists JBI guidance for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Reviewer's Manual on our website.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CAT), in journal clubs and as an educational tool.

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JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____Date_____

Author _____Year_____Record Number _____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2.	Was allocation to treatment groups concealed?	☐	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☐	☐	☐	☐
4.	Were participants blind to treatment assignment?	☐	☐	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7.	Were treatment groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	☐	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
12.	Was appropriate statistical analysis used?	☐	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Explanation for the critical appraisal tool for RCTs with individual participants in parallel groups

How to cite: Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Critical Appraisal Tool for RCTs (individual participants in parallel groups)

Answers: Yes, No, Unclear or Not Applicable

1. **Was true randomization used for assignment of participants to treatment groups?**

   The differences between participants included in compared groups constitutes a threat to the internal validity of a study exploring causal relationships. If participants are not allocated to treatment and control groups by random assignment there is a risk that the allocation is influenced by the known characteristics of the participants and these differences between the groups may distort the comparability of the groups. A true random assignment of participants to the groups means that a procedure is used that allocates the participants to groups purely based on chance, not influenced by the known characteristics of the participants. Check the details about the randomization procedure used for allocation of the participants to study groups. Was a true chance (random) procedure used? For example, was a list of random numbers used? Was a computer-generated list of random numbers used?

2. **Was allocation to groups concealed?**

   If those allocating participants to the compared groups are aware of which group is next in the allocation process, that is, treatment or control, there is a risk that they may deliberately and purposefully intervene in the allocation of patients by preferentially allocating patients to the treatment group or to the control group and therefore this may distort the implementation of allocation process indicated by the randomization and therefore the results of the study may be distorted. Concealment of allocation (allocation concealment) refers to procedures that prevent those allocating patients from knowing before allocation which treatment or control is next in the allocation process. Check the details about the procedure used for allocation concealment. Was an appropriate allocation concealment procedure used? For example, was central randomization used? Were sequentially numbered, opaque and sealed envelopes used? Were coded drug packs used?

3. **Were treatment groups similar at the baseline?**

   The differences between participants included in compared groups constitute a threat to the internal validity of a study exploring causal relationships. If there are differences between

participants included in compared groups there is a risk of selection bias. If there are differences between participants included in the compared groups maybe the 'effect' cannot be attributed to the potential 'cause' (the examined intervention or treatment), as maybe it is plausible that the 'effect' may be explained by the differences between participants, that is, by selection bias. Check the characteristics reported for participants. Are the participants from the compared groups similar with regards to the characteristics that may explain the effect even in the absence of the 'cause', for example, age, severity of the disease, stage of the disease, co-existing conditions and so on? Check the proportions of participants with specific relevant characteristics in the compared groups. Check the means of relevant measurements in the compared groups (pain scores; anxiety scores; etc.). *[Note: Do NOT only consider the P-value for the statistical testing of the differences between groups with regards to the baseline characteristics.]*

4. **Were participants blind to treatment assignment?**

   If participants are aware of their allocation to the treatment group or to the control group there is the risk that they may behave differently and respond or react differently to the intervention of interest or to the control intervention respectively compared to the situations when they are not aware of treatment allocation and therefore the results of the study may be distorted. Blinding of participants is used in order to minimize this risk. Blinding of the participants refers to procedures that prevent participants from knowing which group they are allocated. If blinding of participants is used, participants are not aware if they are in the group receiving the treatment of interest or if they are in any other group receiving the control interventions. Check the details reported in the article about the blinding of participants with regards to treatment assignment. Was an appropriate blinding procedure used? For example, were identical capsules or syringes used? Were identical devices used? Be aware of different terms used, blinding is sometimes also called masking.

5. **Were those delivering treatment blind to treatment assignment?**

   If those delivering treatment are aware of participants' allocation to the treatment group or to the control group there is the risk that they may behave differently with the participants from the treatment group and the participants from the control group, or that they may treat them differently, compared to the situations when they are not aware of treatment allocation and this may influence the implementation of the compared treatments and the results of the study may be distorted. Blinding of those delivering treatment is used in order to minimize this risk. Blinding of those delivering treatment refers to procedures that prevent those delivering treatment from knowing which group they are treating, that is those delivering treatment are not aware if they are treating the group receiving the treatment of interest or if they are treating any other group receiving the control interventions. Check the details reported in the article about the blinding of those delivering treatment with regards to treatment assignment.

Is there any information in the article about those delivering the treatment? Were those delivering the treatment unaware of the assignments of participants to the compared groups?

6. Were outcomes assessors blind to treatment assignment?

If those assessing the outcomes are aware of participants' allocation to the treatment group or to the control group there is the risk that they may behave differently with the participants from the treatment group and the participants from the control group compared to the situations when they are not aware of treatment allocation and therefore there is the risk that the measurement of the outcomes may be distorted and the results of the study may be distorted. Blinding of outcomes assessors is used in order to minimize this risk. Check the details reported in the article about the blinding of outcomes assessors with regards to treatment assignment. Is there any information in the article about outcomes assessors? Were those assessing the treatment's effects on outcomes unaware of the assignments of participants to the compared groups?

7. Were treatment groups treated identically other than the intervention of interest?

In order to attribute the 'effect' to the 'cause' (the treatment or intervention of interest), assuming that there is no selection bias, there should be no other difference between the groups in terms of treatment or care received, other than the manipulated 'cause' (the treatment or intervention controlled by the researchers). If there are other exposures or treatments occurring at the same time with the 'cause' (the treatment or intervention of interest), other than the 'cause', then potentially the 'effect' cannot be attributed to the examined 'cause' (the investigated treatment), as it is plausible that the 'effect' may be explained by other exposures or treatments occurring at the same time with the 'cause' (the treatment of interest). Check the reported exposures or interventions received by the compared groups. Are there other exposures or treatments occurring at the same time with the 'cause'? Is it plausible that the 'effect' may be explained by other exposures or treatments occurring at the same time with the 'cause'? Is it clear that there is no other difference between the groups in terms of treatment or care received, other than the treatment or intervention of interest?

8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?

For this question, follow up refers to the time period from the moment of random allocation (random assignment or randomization) to compared groups to the end time of the trial. This critical appraisal question asks if there is complete knowledge (measurements, observations etc.) for the entire duration of the trial as previously defined (that is, from the moment of random allocation to the end time of the trial), for all randomly allocated participants. If there is incomplete follow up, that is incomplete knowledge about all randomly allocated

participants, this is known in the methodological literature as the post-assignment attrition. As RCTs are not perfect, there is almost always post-assignment attrition, and the focus of this question is on the appropriate exploration of post-assignment attrition (description of loss to follow up, description of the reasons for loss to follow up, the estimation of the impact of loss to follow up on the effects etc.). If there are differences with regards to the loss to follow up between the compared groups in an RCT, these differences represent a threat to the internal validity of a randomized experimental study exploring causal effects, as these differences may provide a plausible alternative explanation for the observed 'effect' even in the absence of the 'cause' (the treatment or intervention of interest). When appraising an RCT, check if there were differences with regards to the loss to follow up between the compared groups. If follow up was incomplete (that is, there is incomplete information on all participants), examine the reported details about the strategies used in order to address incomplete follow up, such as descriptions of loss to follow up (absolute numbers; proportions; reasons for loss to follow up) and impact analyses (the analyses of the impact of loss to follow up on results). Was there a description of the incomplete follow up (number of participants and the specific reasons for loss to follow up)? It is important to note that with regards to loss to follow up, it is not enough to know the number of participants and the proportions of participants with incomplete data; the reasons for loss to follow up are essential in the analysis of risk of bias; even if the numbers and proportions of participants with incomplete data are similar or identical in compared groups, if the patterns of reasons for loss to follow up are different (for example, side effects caused by the intervention of interest, lost contact etc.), these may impose a risk of bias if not appropriately explored and considered in the analysis. If there are differences between groups with regards to the loss to follow up (numbers/proportions and reasons), was there an analysis of patterns of loss to follow up? If there are differences between the groups with regards to the loss to follow up, was there an analysis of the impact of the loss to follow up on the results? [Note: Question 8 is NOT about intention-to-treat (ITT) analysis; question 9 is about ITT analysis.]

9. Were participants analyzed in the groups to which they were randomized?

This question is about the intention-to-treat (ITT) analysis. There are different statistical analysis strategies available for the analysis of data from randomized controlled trials, such as intention-to-treat analysis (known also as intent to treat; abbreviated, ITT), per-protocol analysis, and as-treated analysis. In the ITT analysis the participants are analyzed in the groups to which they were randomized, regardless of whether they actually participated or not in those groups for the entire duration of the trial, received the experimental intervention or control intervention as planned or whether they were compliant or not with the planned experimental intervention or control intervention. The ITT analysis compares the outcomes for participants from the initial groups created by the initial random allocation of participants to those groups. Check if ITT was reported; check the details of the ITT. Were participants analyzed in the groups to which they were initially randomized, regardless of whether they actually participated in those groups, and

regardless of whether they actually received the planned interventions? *[Note: The ITT analysis is a type of statistical analysis recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement on best practices in trials reporting, and it is considered a marker of good methodological quality of the analysis of results of a randomized trial. The ITT is estimating the effect of offering the intervention, that is, the effect of instructing the participants to use or take the intervention; the ITT it is not estimating the effect of actually receiving the intervention of interest.]*

10. Were outcomes measured in the same way for treatment groups?

If the outcome (the 'effect') is not measured in the same way in the compared groups there is a threat to the internal validity of a study exploring a causal relationship as the differences in outcome measurements may be confused with an effect of the treatment (the 'cause'). Check if the outcomes were measured in the same way. Same instrument or scale used? Same measurement timing? Same measurement procedures and instructions?

11. Were outcomes measured in a reliable way?

Unreliability of outcome measurements is one threat that weakens the validity of inferences about the statistical relationship between the 'cause' and the 'effect' estimated in a study exploring causal effects. Unreliability of outcome measurements is one of the different plausible explanations for errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment ('cause'). Check the details about the reliability of measurement such as the number of raters, training of raters, the intra-rater reliability, and the inter-raters reliability within the study (not as reported in external sources). This question is about the reliability of the measurement performed in the study, it is not about the validity of the measurement instruments/scales used in the study. *[Note: Two other important threats that weaken the validity of inferences about the statistical relationship between the 'cause' and the 'effect' are low statistical power and the violation of the assumptions of statistical tests. These other two threats are explored within Question 12).]*

12. Was appropriate statistical analysis used?

Inappropriate statistical analysis may cause errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment ('cause'). Low statistical power and the violation of the assumptions of statistical tests are two important threats that weaken the validity of inferences about the statistical relationship between the 'cause' and the 'effect'. Check the following aspects: if the assumptions of statistical tests were respected; if appropriate statistical power analysis was performed; if appropriate effect sizes were used; if appropriate statistical procedures or methods were used given the number and type of dependent and independent variables, the number of study groups, the nature of the

relationship between the groups (independent or dependent groups), and the objectives of statistical analysis (association between variables; prediction; survival analysis etc.).

13. Was the trial design appropriate for the topic, and any deviations from the standard RCT design accounted for in the conduct and analysis?

Certain RCT designs, such as the crossover RCT, should only be conducted when appropriate. Alternative designs may also present additional risks of bias if not accounted for in the design and analysis.

Crossover trials should only be conducted in people with a chronic, stable condition, where the intervention produces a short term effect (i.e. relief in symptoms). Crossover trials should ensure there is an appropriate period of washout between treatments.

Cluster RCTs randomize groups of individuals, forming 'clusters.' When we are assessing outcomes on an individual level in cluster trials, there are unit-of-analysis issues, as individuals within a cluster are correlated. This should be taken into account by the study authors when conducting analysis, and ideally authors will report the intra-cluster correlation coefficient.

Stepped-wedge RCTs may be appropriate when it is expected the intervention will do more good than harm, or due to logistical, practical or financial considerations in the roll out of a new treatment/intervention. Data analysis in these trials should be conducted appropriately, taking into account the effects of time.

The Joanna Briggs Institute Critical Appraisal tools
for use in JBI Systematic Reviews

Checklist for Cohort Studies

http://joannabriggs.org/research/critical-appraisal-tools.html

www.joannabriggs.org

The Joanna Briggs Institute

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THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

Author _____Year_____Record Number _____.

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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_____

THE JOANNA BRIGGS INSTITUTE

Explanation of cohort studies critical appraisal

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Cohort studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. **Were the two groups similar and recruited from the same population?**

   Check the paper carefully for descriptions of participants to determine if patients within and across groups have similar characteristics in relation to exposure (e.g. risk factor under investigation). The two groups selected for comparison should be as similar as possible in all characteristics except for their exposure status, relevant to the study in question. The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants.

2. **Were the exposures measured similarly to assign people to both exposed and unexposed groups?**

   A high quality study at the level of cohort design should mention or describe how the exposures were measured. The exposure measures should be clearly defined and described in detail. This will enable reviewers to assess whether or not the participants received the exposure of interest.

3. **Was the exposure measured in a valid and reliable way?**

   The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

   Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. **Were confounding factors identified?**

   Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic

factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

5. **Were strategies to deal with confounding factors stated?**

   Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of statistical methods as regression methods such as logistic regression are usually employed to deal with confounding factors/variables of interest.

6. **Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?**

   The participants should be free of the outcomes of interest at the start of the study. Refer to the 'methods' section in the paper for this information, which is usually found in descriptions of participant/sample recruitment, definitions of variables, and/or inclusion/exclusion criteria.

7. **Were the outcomes measured in a valid and reliable way?**

   Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

   Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?

The appropriate length of time for follow up will vary with the nature and characteristics of the population of interest and/or the intervention, disease or exposure. To estimate an appropriate duration of follow up, read across multiple papers and take note of the range for duration of follow up. The opinions of experts in clinical practice or clinical research may also assist in determining an appropriate duration of follow up. For example, a longer timeframe may be needed to examine the association between occupational exposure to asbestos and the risk of lung cancer. It is important, particularly in cohort studies that follow up is long enough to enable the outcomes. However, it should be remembered that the research question and outcomes being examined would probably dictate the follow up time.

9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?

It is important in a cohort study that a greater percentage of people are followed up. As a general guideline, at least 80% of patients should be followed up. Generally a dropout rate of 5% or less is considered insignificant. A rate of 20% or greater is considered to significantly impact on the validity of the study. However, in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected. A decision on whether to include or exclude a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether dropout rates were comparable in the exposed and unexposed groups.

Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study. Look for clear and justifiable description of why people were left out, excluded, dropped out etc. If there is no clear description or a statement in this regards, this will be a 'No'.

10. Were strategies to address incomplete follow up utilized?

Some people may withdraw due to change in employment or some may die; however, it is important that their outcomes are assessed. Selection bias may occur as a result of incomplete follow up. Therefore, participants with unequal follow up periods must be taken into account in the analysis, which should be adjusted to allow for differences in length of follow up periods. This is usually done by calculating rates which use person-years at risk, i.e. considering time in the denominator.

11. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of cohort studies should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Appendix IV: Explanation for given answers in the critical appraisal tools

The following is the set to answer to the questions in the JBI critical appraisal check list for RCTs and cohort studies. To give each question yes, no, unclear or not applicable to the RCT checklist questions the criteria were set for each question. For the RCT check list tool, the criteria to give the score are:

Qestion1. Given yes if the random method was stated, no if stated not random, and unclear if state random, but no method was clearly written.

Question 2. Given ‘Yes’ if the concealed method was stated, ‘No’ if concealed method was stated not concealed, and ‘Unclear’ if there was no clear statement about concealed method.

Question 3. Given ‘Yes’ if participant characteristics were similar, ‘No’ if not and ‘Unclear’ if not report at all.

Question 4. Given ‘Yes’ if stated participant were blinded, given ‘No’ if stated not blinded and given ‘Unclear if not stated.

Question 5. Given ‘Yes’ if stated investigators were blinded, given ‘No’ if stated investigator were not blinded, and given ‘Unclear if not stated.

Question 6. Given ‘Yes’ if the stated that the outcomes assessor was blinded, given ‘No’ if stated not blinded, and given ‘Unclear’ if not stated.

Question 7. Given ‘Yes’ if participants were treated/cared similarly and given ‘No’ if were not

Question 8. Given ‘Yes’ if stated all participants completed the study, if all participant data were analysed and if there was a number of drop out participant with reasons provided for post assignment attrition, and the numbers in both groups (intervention and comparator) were comparable, given ‘No’ if stated there was a number for post assignment attrition and the numbers were not comparable, given ‘Unclear’ if not stated.

Question 9. Given ‘Yes’ if:

- The participant data were analysed into the group participant allocated to, and all the participants completed the study and the participant data were analysed according to statistic concept of intention to treat (ITT) to give an unbiased estimate of the treatment.[172]
- There was a dropout or withdrawn number or missing outcome data, or outcome data were unobtainable (met the exclusion criteria protocol during the study) or missing data was dealt with by using the last observation carried forward or used imputation technique [173] or analysed data as per protocol (PP) analysis (data being analysed only from the participant who completed the study.[174]

Given 'No' if there was a dropout or incomplete, the data were not analysed, and the study authors stated it. Given 'Unclear' if there was no report of numbers of dropout, in-completed study, and no full datasets were clearly written.

Question 10. Given 'Yes' if the intervention and comparator group used the same tool, scale and same duration of measurement, given 'No' if the primary study authors reported not using the same tool, scale and duration of measurement and given 'Unclear' if not stated.

Question 11. Given 'Yes' if the investigator/ rater quality was stated (experts/ raters were trained to use the measurement tool), given 'No' if the investigator quality reported as non-expert and given 'Unclear' if there was no report.

Question 12. Given 'Yes' if appropriate statistical analysis was used and given 'No' if inappropriate statistic was used.

Question 13. Given 'Yes' if the study design was appropriate to topic and given 'No' if the study design was not appropriate to the topic.

To give each question yes, no, unclear or not applicable to the cohort study check list questions, the criteria were set for each question. For the cohort study check list tool, the criteria to give the score are following.

Question 1. Given 'Yes' if the two group is similar in their characteristics or if a matched paired, or a crossover design, given 'No' if the participant characteristic were not similar, given 'Unclear 'if there was no report of participant characteristics.

Question 2. Given ‘Yes’ if the exposures (intervention) and non-exposure (comparator/ control) measured in similar way, given ‘No’ if stated not measured similar and given ‘Unclear’ if no report.

Question 3. Given ‘Yes’ if exposure measured in a reliable way, given ‘No’ if stated it was not and given ‘Unclear’ if there was no report.

Question 4. Given ’Yes’ if stated confounding factors were identified, given ‘No’ if confounder stated not identified and given ‘Unclear if there was no report of confounders.

Question 5. Given ’Yes’ if strategies to deal with confounding factors were stated, given ‘No, if stated confounding factor not being identified/ controlled, given ‘Unclear’ if no report of possible confounders.

Question 6. Given ‘Yes’ if stated groups/participants free of the outcome at the start of the study, given ‘No, if stated not free from outcome/s, given ‘Unclear’ if not stated and given ‘Not applicable’ if not relevant to the study design or justification of evidence indiscernible.

Question 7. Given ‘Yes’ if the outcome measured in a valid and reliable way, given ‘No’ if stated not and given ‘Unclear’ if no report of measurement details.

Question 8. Given ‘Yes’ if the follow up time reported and sufficient to be long enough for outcomes to occur and given ‘No’ if stated not sufficient to be long enough for outcomes to occur.

Question 9. Given ‘Yes, if follow up complete and if not, the reasons for loss of follow up described and explored and given ‘No’ if the follow up not completed and the reason for loss of follow up not given.

Question 10. Given ‘Yes’ if strategies to address incomplete follow up utilized either used last outcome forward or as per protocol, given ‘No’ if none of the strategies were stated and given ‘Not applicable if there was no dropout or in complete study participant.

Question 11. Given ’Yes’ if appropriate statistical test to analyse the data was used, given ‘No’ if not.

Appendix V: Joanna Briggs Institute Data Extraction Tool

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix VI: Ventilator setting strategies

Study	Ventilator setting strategies												
	Assistance level		Categorized level of setting		ITS		ETS		PEEPe		Independent variables	Identical setting	Constant setting
	NAVA gain ($cmH_2O/\mu V$)	PS level (cmH_2O)	NAVA	PSV	NAVA	PSV	NAVA	PSV	NAVA	PSV			
Ferreira (2017)	10.3(5.2-22.9)	5	Optimal	NR	Edi 0.5µV	Varies to individual	70% Edi-peak	13-52% of peak inspiratory flow	5	5	Assistance level	Paw	PEEPe, PS and FiO_2
Costa (2017)	No data reported, setting to achieve V_T 6-8ml/kg ideal body weight	No data reported, setting to achieve V_T 6-8ml/kg ideal body weight	Optimal	Optimal	Edi 0.5µV above base line plus default	50% change of bias flow (2PLM)	70% Edi-peak	Tailored to patient to optimize PVI	Tailored to individual patient clinical required	Tailored to individual patient clinical required	Mode with optimal variable setting with four different Remifenta-nil infusion rates	V_T 6-8ml/kg ideal body weight (V_T and Edi as close as possible)	FiO_2 & PEEPe according to local guidelines
Beloncle (2017)	Edi-max:16.8 (14-22.3)	9(8-10); step2	Optimal (step 4)	Optimal Step 1, 2 and 3	Adjusted to reduce ineffective effort	Adjusted to optimize PVS	70% Edi-peak	47.5% (40-53) %of peak inspiratory flow	8(7.25-9.75)	8(5.75-8)	Level of assistance	Paw	PS
Demoule (2017)	1.93±1.15	27±1	Optimal	Optimal	Edi 0.5µV above base line	50% change of bias flow 2LPM	70% preceding Edi-peak	Tailored to patient to optimize PVI	Constant (high PEEPe and low FiO_2	Constant (high PEEPe and low FiO_2	Mode with optimal variable setting	VT 6-8ml/kg ideal body weight & peak Paw	FiO2 & PEEPe according to local guidelines
Di mussi (2016)	1.35±0.38	11.4±2.1	Optimal	Optimal	Edi 0.5µV plus, default	Flow by 5 au (Servo-i)	70% Preceding Edi-peak	30% of peak inspiratory flow (default)	7.5±1.7	7.9±1.4	Mode with optimal variable setting	V_T 5-8ml/kg PBW	PEEPe, FiO_2 (NAVA: 43.1±6.3) (PSV: 45.4±9.4)

Study	Ventilator setting strategies												
	Assistance level		Categorized level of setting		ITS		ETS		PEEPe		Independent variables	Identical setting	Constant setting
	NAVA gain ($cmH_2O/\mu V$)	PS level (cmH_2O)	NAVA	PSV	NAVA	PSV	NAVA	PSV	NAVA	PSV			
Carteaux (2016)	N aka NAVA N1: 56% (49-60) N2: 74% (70-83) N4: 83% (81-86)	P aka PSV P7: 33% (24-47) P10: 46% (35-56) P25: 82% (72-90)	Low Optimal High	Low Optimal High	Edi 0.5μV & default flow at 1LPM	Flow trigger: lowest possible	NR	25% of peak inspiratory flow	6±1.4	6±1.4	Mode with optimal variable setting with NAVA gain 9 levels and PSV 5 levels	PEEPe set by attending clinician	PEEPe
Schmidt (2015)	N aka NAVA N50:0.6(0.4-0.9) N100: 1.3(0.8-1.8) N150: 1.9(1.2-2.7)	P aka PSV P50: 7.0(7.0-7.2) P100: 14.0(11.5-15.2) P150: 21.0(17.2-21.7)	Low Optimal High	Low Optimal High	Above the base line noise avoiding auto trigger	Flow trigger: lowest possible without inducing auto trigger	At 70% Edi-peak	30% of peak inspiratory flow (default)	4(4-5)	4(4-5)	Modes with 3 levels of assistance	V_T 6-8ml/kg PBW; comparable Paw-mean observed	FiO_2 &PEEPe
Doorduin (2015)	1.93±1.15	11.9±3.2	Optimal	Optimal	Edi-ON: 0.5μV of increasing Edi	P-ON detected by increased of Paw>3 cmH_2O	Edi-OFF: detect Edi decreased to 70% Edi-peak	Decrease in Paw	14.5±2.1	14.5±2.1	Mode with optimal variable setting	V_T 6ml/kg PBW, Paw	PEEPe (higher PEEPe & lower FiO_2)
Liu (2015)	PSN aka NAVA NAVA-ZEEP	PSP aka PSV PSV-ZEEP	Low	Low	Edi 0.5μV	Flow trigger 1LPM&	70% preceding Edi-peak	30% of peak inspiratory flow (default)	PEEPe 0%, 40%, 80% &120%	PEEPe 0%, 40%, 80% &120%	Mode with & 4 levels of PEEPe	V_T 6ml/kg PSN pressure limit same as	PSN pressure max

Study	Ventilator setting strategies												
	Assistance level		Categorized level of setting		ITS		ETS		PEEPe		Independent variables	Identical setting	Constant setting
	NAVA gain ($cmH_2O/\mu V$)	PS level (cmH_2O)	NAVA	PSV	NAVA	PSV	NAVA	PSV	NAVA	PSV			
	NAVA-PEEe40% NAVA-PEEPe80% NAVA-PEEP120%	PSV-PEEpe40% PSV-PEEPe80% PSV-PEEPe120%	Optimal High	Optimal High		Inspiratory rise time: 0. 05 second						PSP (Paw-peak above PEEPe)	$15cmH_2O/\mu V$ & Paw-peak above PEEPe
Yonis (2015)	6	12.5(4-20)	Optimal	Optimal	Edi 0.5µV plus, default	Flow trigger (set to optimize PVI)	Fixed at 70% Edi-peak	30% (21-40%) of peak inspiratory flow	PEEPe was adapted to PEEPi and ETS	PEEPe was adjusted to PEEPi and ETS	Mode with optimal variable setting	PEEPe, V_T 6-8ml/kg& Paw-peak	PEEPe
Vaschett0 (2014)	Awake: defined at this level, NR continuous data Light sedation Deep sedation	Awake: 11.7±2.5 all level Light sedation Deep Sedation	Optimal Optimal Optimal	Optimal Optimal Optimal	Edi 0.5µV plus, default	Level 5 equals 50% of 2LPM	Fixed at 70% Edi-peak	30% of peak inspiratory flow	8.4±2.4	8.4±2.4	Mode with optimal variable setting and 3 levels of sedation in each mode	V_T 6-8ml/kg, identical VT& Edi	FiO_2 & PEEPe
Mauri (2013)	1.1±0.6	12±2	Optimal	PSV1% : low PSV30 %: optimal	Edi 0.5µV plus default	Pressure at -2cmH2O & flow based at 2-5 LPM	At 70% of Edi peak	PAS1at 1% PSV30 30% of flow peak volume	NR (constant	NR (constant)	One assist level with 3 levels of ETS (NAVA 1, PSV1 and PSV30)	V_T as pre-clinical setting for optimal PSV, V_T 3-5ml/kg, Paw<30, RR<35	FiO_2, PEEPe and ECMO blood and Gas flow

Study	Ventilator setting strategies												
	Assistance level		Categorized level of setting		ITS		ETS		PEEPe		Independent variables	Identical setting	Constant setting
	NAVA gain ($cmH_2O/\mu V$)	PS level (cmH_2O)	NAVA	PSV	NAVA	PSV	NAVA	PSV	NAVA	PSV			
Patroniti (2012)	NAVA0.5 NAVA1.0 NAVA1.5 NAVA2.0 NAVA2.5 NAVA3.0 NAVA4.0	PSV4 PSV8 PSV10 PSV16	Low Low Optimal Optimal High High	Low Optimal Optimal High	Above the base line Edi	Flow lowest possible without auto triggering	Edi decreased at 70% of its inspiratory peak	30% of peak inspiratory flow	8.1 ±2.2	8.1 ±2.2 adjusted based on PaO2 responses & respiratory compliance	Mode with optimal variable setting with NAVA gain 7 levels and PSV 4 levels	Alarm limited Paw-peak at 35 cmH2O	FiO_2 & PEEPe
Piquillo ud (2011)	2.2 ± 1.8	13±3	Optimal	Optimal	Edi 0.5µV And default	-Pressure trigger -4 to -5 cmH2O (2/22) -Flow trigger 1.2 LPM --Pressure slope 100-150ms	70%of Edi peak	25 to 30% of peak inspiratory flow	7±2	7±2	Assistance level (optimal level of assistance in each mode); PSV perform twice with same setting	Paw V_T: NAVA 6.6 (6.1-7.9) PSV1:	FiO_2, PEEPe, ETS & ITS
Terzi (2010)	NAVA100 NAVA120 NAVA140 NAVA160	PSV100 PSV120 PSV140 PSV160	Optimal High High High	Optimal High High High	Edi 0.5 µV and default	Flow lowest possible without auto triggering	NR	inspiratory flow decreases to <25 % of peak flow	5.37±1.42	5.27±1.42	One level of assistance	Peak pressure, V_T 6-8ml/kg	FiO_2 & PEEPe
Spahija (2010)	NAVA-low +PS 7.6±4.6	PSV- low +PS 7.6±4.6	High	High	Above the base line noise	Pressure -1cmH_2O below	At 70% of Edi peak	Servo 300 flow cycling fixed at 5%	5.8±1.6	5.8±1.6	Assistance level plus	V_T 6-8ml/kg, and Paw-peak	FiO_2 & PEEPe

Study	Ventilator setting strategies										Independent variables	Identical setting	Constant setting
	Assistance level		Categorized level of setting		ITS		ETS		PEEPe				
	NAVA gain ($cmH_2O/\mu V$)	PS level (cmH_2O)	NAVA	PSV	NAVA	PSV	NAVA	PSV	NAVA	PSV			
	NAVA-high +PS 17.4±4.3	PS50: 5.7±2	Low	Low	avoiding auto triggering	PEEPe, Rise time set 1% of respiratory cycle time		peak inspiratory flow			additional PS		
Colombo (2008)	NAVA50:0.6±0.6 NAVA100: 1.3±1.2 NAVA150: 1.9±1.8	PS50: 5.7±2 PS100: 11±3.2 PS150: 16.3±4.6	Low Optimal High	Low Optimal High	'First serves first'; NR for NAVA ITS	Lowest possible avoid auto trigger	Edi fell to 70% its peak	30% of peak inspiratory flow	NAVA50: 9.7±3.3 NAVA100: 9.6±3.2 NAVA150: 9.6±3.2	PSV50: 9.5±3.3 PSV100: 9.6±3.2 PSV150: 9.6±3.2	Mode with 3 levels of assistance	-Inspiratory peak – Paw - V_T6-8ml/kg PBW	FiO_2& PEEPe

NAVA: Neurally Adjusted Ventilatory Assist, PSV: pressure support ventilation, ITS: inspiratory trigger sensitivity, ETS: expiratory trigger sensitivity, PS pressure support, Edi: Electrical activity of diaphragm, μV: microvolt, cmH_2O: centimeter of water, NR: not report, LPM: litter per minute, PVI: patient ventilator interaction, V_T: tidal volume, FiO_2: fraction of oxygen, PEEPe: external positive end expiratory pressure, PEEPi: intrinsic positive end expiratory pressure, ZEEP: zero end expiratory pressure, SBT: spontaneous breathing trial, PBW: predicted body weight, Paw: airway pressure, PaO_2: partial pressure of oxygen, ms: millisecond.

Appendix VII: Demographic characteristics of participants in included studies

Study	Etiology of ARF (n)	Sample size (n) Age (years)	Gender (male/ female)	PEEPe	Sedation score/ medications	APACHE-II/ Cstrs	Mean FiO2	SAPS-II/SOFA	Duration of IMV (Day/s) at inclusion
Costa (2017)[148]	Post-operative ARF (9) Pneumonia (2) Exacerbation of COPD (2)	(13) 58.9±15.86	M10/ F3	NR (PEEPe unmodified)	RSS 2 to 3 (2pt had RSS 4) Remifentanil mcg/kg/min	NR/NR	NR: Unmodified during the study	NR/NR	NR but on partial vent support <72h priori included
Ferreira (2017) [24]	COPD (7), pneumonia (5), Plural effusion (1) Extra- pulmonary (7)	(20) 64.45±17.12	NR	Mean: 6.7±1.50S, PS: 9.85±2.80	NR/NR	NR/NR	0.34±0.06	SOFA III: 64.45±17.12	>48h Mean= 6.20±2.78
Beloncle (2017)[21]	History of: COPD (6); Obesity (5); Bronchiectasis (1); left ventricular dysfunction (1); Interstitial pulmonary disease (1)	(11) Median & IQR =70 (68-80)	M7/F4	Step1: 8(5.75-8) Step2: 8(5.75-8) Step3: 8(7.25-9.75) Step4: 8(7.25-9.75)	NR/NR	20(17-23.5)/; Cstrs: NR	0.5(0.4-0.5)	SOFA: 5(3.5-8)	Expected IMV for >24h; Median &IQR=4(1-13)
Demoule (2016)[109]	NAVA/PSV: De no vo: (34/38), post-operative: (13/13) acute on chronic: (12/12), acute cardiogenic pulmonary edema: (3/3)	NAVA (66) PSV (62) Median & IQR:66 (57-77)	NAVA: M47/F15 PSV:M39 /27	NAVA:6(5-8) PSV:6(5-8)	RASS at most 4/ medication NR	NR/NR	NR but report PaO_2/FiO_2 NAVA=235(185-265); PSV=227(192-286)	SAPS 2: NAVA=44(36-64); PSV=43.5(34-59)	>24h NAVA=4(2-8); PSV=5(3-8)

Study	Etiology of ARF (n)	Sample size (n) Age (years)	Gender (male/ female)	PEEPe	Sedation score/ medications	APACHE-II/ Cstrs	Mean FiO2	SAPS-II/SOFA	Duration of IMV (Day/s) at inclusion
Di Mussi (2016)[10]	Pulmonary: NAVA (7); PSV (7) Extra pulmonary: NAVA (6), PSV (5)	NAVA (13): 66.8± 17.3 PSV (12) :69.8±15	NR	NR	RASS 0 to -1 with no or moderate sedation using Remifentanil, and/or Midazolam and /or Propofol	NAVA: 13.2±4.3 PSV: 14.6±3.4; Cstrs: NR	NAVA: 43.1±6.3 PSV: 45.4±9.4	NR/NR	At least 72h; NAVA: 5.1±1.7d PSV: 5.1±1.3
Carteaux (2016)[46]	ARDS (9) Cardiogenic pulmonary edema (2)	(11) 69.8±13.9	M5/ F6	NR	RASS -3 to 1 No patient received any drug during the study	52.46±1.420.2; Cstrs: NR	FiO_2:0.4±0.1 PaO_2/FiO_2: 261.9±92.1	SAP II: 52.36±20.2 /NR	16±11
Doorduin (2015)[151]	ARDS (12)	(12) 64±11.2	NR	NR	RASS-5 to 0	NR/NR	FiO_2: 0.53±0.12 PaO_2/FiO_2: 143.5±43.0	NR/NR	6.9±9
Liu (2015)[140]	COPD (12)	(12) 78.8±8.6	NR	5.8±1.1	RSS 2 to 3; awake and able to follow commands No sedation or minimal analgesia with low dose of morphine <3 mg/h, by continuous intravenous infusion	APACHE-II:32.4±4.5, Cstrs:33.1±8.1	40.8±2.9	NR/NR	3.8±2.1
Schmidt (2015)[149]	ARDS (4) COPD (3) Pneumonia (9)	(16) 69.7±8.9	M10/F6	4 (4-5)	Stop>6 h	NR/NR	FiO2:0.5 (0.5-0-5)	SAP-II: 55 (48-64) /NR	7.9±4.9
Yonis (2015)[20]	Medical (14), surgical (13) & trauma (3) known pulmonary disease 56.6%	(30) 66.3±11	M19/F11	Adjusted to PEEPi (NR continuous data)	Without sedation	NR/NR	PaO2/FiO2 PSV: 203.15 (113.2-389.3)	SAP II: 58.6±20.6 /NR	NR

Study	Etiology of ARF (n)	Sample size (n) Age (years)	Gender (male/ female)	PEEPe	Sedation score/ medications	APACHE-II/ Cstrs	Mean FiO2	SAPS-II/SOFA	Duration of IMV (Day/s) at inclusion
	ARDS 50%; Cardiac 36.6%						NAVA: 254.3(136.4-409.6)		
Vaschetto (2014)[152]	Pulmonary (12) Extra pulmonary (2)	(16) 66.6±14	M10/F4	NR	RSS: Awake: 2.2±0.4; Light: 3.9±1.3; Deep: 6.0±0 (BIS of 40)/ Propofol	NR/NR	0.42±0.1 at inclusion	NR/NR	NR
Mauri (2013)[16]	10 ARDS with low respiratory system compliance	(10) 46±13	M7/F3	NR	RASS -1 to 0 with no sedation	APACHE+II:NR; Cstrs 18 ±8 (ml/cmH_2O)	Identical all settings:0.55± 0.20; PaO2/FiO2: approximately identical: 244±116	NR/NR	23±17
Patroniti (2012)[147]	Pulmonary (10) Extra pulmonary (5)	(15) 68±2	M9/F6	8.13±2.2	RSS 2 to 3 Midazolam or Propofol and either Remifentanil or Fentanyl	NR/NR	0.43± 0.1 PaO_2/FiO_2:247.07±80.8	NR/NR	15±12
Piquilloud (2011)[1]	Pulmonary (9) Others (13)	(11) 66± 12	M7/F15	7±2	NR	NR/NR	0.43±0.17	SAP II: 48±12 /NR	3±2
Terzi (2010)[2]	ARDS patients (11)	(11) 56.1±11.1	M10/F1	5.27±1.4	RSS 2 to 3 received Propofol only,	NR/NR	PaO_2/FiO_2=101.636 ±31.3	NR/ SOFA 8.9±2,6	14±5.4
Spahija (2010)[65]	COPD (10) Extra pulmonary (4)	(14) 69±10	M10/F1	5.9±3.7	Stopped sedation>4h	NR/ Cstrs 0.063 ±0.02 L/cm, mean (SD)	0.33±0.04	NR/NR	4.9±2.6

Study	Etiology of ARF (n)	Sample size (n) Age (years)	Gender (male/ female)	PEEPe	Sedation score/ medications	APACHE-II/ Cstrs	Mean FiO2	SAPS-II/SOFA	Duration of IMV (Day/s) at inclusion
Colombo (2008)[22]	Pulmonary (4) Extra pulmonary (10)	(16) 55.4±15.8	M12/F2	9.5±3.5	RSS 3 get either Propofol alone or with Fentanyl or Remifentanil	NR/NR	0.375±0.6	NR/NR	7.21±5.1

Continuous data reported as mean and standard deviation, otherwise stated, ARDS: acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease, PSV: pressure support ventilation, NAVA: Neurally adjusted ventilatory assist, NR: not report, PEEPe: external positive end expiratory pressure, RASS: Richmond Agitation Sedation Scale, RSS: Ramsey Sedation Scale, M:male, F: female, APACHE(Acute Physiology and Chronic Health Enquiry, n= number of participant, IQR: interquartile range Cstrs: static respiratory system compliance, LIS: Lung injury score.

Appendix VIII: Details of additional data obtain from included study authors

Studies	Contact details	Queries	Response/outcome data provided
Costa (2017)	longhini.federico@gmail.com	Number of participants who have AI>10%	The principle investigator provided a raw dataset.
Demoule (2015)	alexandre.demoule@psl.aphp.fr	Relevant outcome data 1. Total time for asynchrony prevalence data record 2. Inspiratory trigger sensitivity setting for both modes	1. Dyssynchrony prevalence data were recorded 20 minutes in each time point at 12,24,36 and 48 hours that in total it was 80 minutes in each group of participants. 2. Inspiratory trigger sensitivity for each patient in NAVA was set at 0.5µV and adjusted by the physician in charge if required according to the local guideline. 3. Inspiratory trigger sensitivity for PSV setting was unavailable, however; the flow trigger was used.

Studies	Contact details	Queries	Response/outcome data provided
Mauri (2013)	ResearchGate via message to Dr. Tommaso Mauri	Continuous data for AI in each mode	The AI of Edi number is correct, but that is not the normal AI as in Thille 2006 publication. In facts, we counted respiratory rate by Edi deflections and not on Paw waveform. The values of the classical AI were: PSV30: MEAN 51 (SD 18) PSV1: 44 (16) NAVA: 16 (9)
Spahija (2012)	"Dr. Jadranka Spahija" jadranka.spahija@mcgill.ca	Clarified au (arbitrary unit) and study design (wash out period)	'au 'of Edi (EAdi) meant arbitrary unit, not to be quantified with a microvolt
Terzi (2010)	ResearchGate via message to Dr. Terzi	To clarify a statistic report, requested for a continuous data of PVA and ventilator ETS	1. Is due to mixed model 2. Cycling off 70%
Colombo (2008)	paolo.navalesi@med.unipmn.it	Continuous data of AI%	Continuous and dichotomous data were provided by Davide Colombo
Doorduin (2015)	ResearchGate	1. What random method was used in the study? In the study protocol on the page 182 stated that " were randomly applied. 2. On the page 186 in the patient-ventilator interaction heading, would you be able to provide the data of % of the patient trigger and ventilator trigger in PSV and NAVA mode? 3. In table 4 on the page 187, Which data are mean standard error, and which are medians? I ask these questions because the mean is required for estimating the effect of intervention. 4. Was any statistic method being used to test for carry over effect in this crossover trial?	1.A simple randomization by drawing envelopes to determine the order of ventilation modes. 2. During PSV and NAVA mode all breaths were patient triggered. 3. Data with the ±sign are means and data with a range between brackets are medians. 4. Randomization was used to minimize carry over effect, but no statistic tests.

Appendix IX: Inclusion and exclusion criteria for included studies' participants

Study	Inclusion criteria	Exclusion criteria
Costa (2017)[148]	1)Patient ≥ 18 years old, 2) Orally intubated and undergoing partial ventilatory support for a period ≤ 72 h, 3)Received only short acting sedative agents (i.e., Propofol and/or Remifentanil); required to be conscious, as indicated by a Glasgow Coma Scale (GCS) of 11 and a Ramsay sedation Score of 1.	1) Hemodynamic instability, as defined by a systolic arterial pressure<90 mmHg or mean arterial pressure< 60 mmHg, or use of vasoactive agents despite adequate fluid replacement 2) Contraindication to the EAdi catheter positioning (i.e., history of oesophageal varices or gastroesophageal bleeding or gastroesophageal surgery in previous 12 months) 3) Renal failure (i.e., serum creatinine ≥ 110 µmol/L) 4) Core temperature greater than 38 ° 5)Pregnancy; 6) recent history of traumatic injuries 6) Recent history of traumatic injuries or surgical wound causing major painful stimuli 7) Refused consent.
Ferreira (2017)[24]	1)Received IMV ≥48 h and the ICU team considered to be ready to undergo an SBT. 2) It must be the first SBT attempt.	1) Age <18 years, is pregnant, and tracheotomized 2) participation in other clinical trials 1) Contraindications to the placement of the oesophageal catheter (nasal pathologies, facial trauma or burns, or oesophageal varicose or gastro oesophageal bleeding in the past 30 days
Belonecle (2017)[21]	1) Ventilated using PSV for an expected duration of ventilation for >24 hours 2) known or suspected history of chronic pulmonary obstructive (COPD) or restrictive disease, obesity (defined as body mass index (BMI) ≥ 30 kg.m-2) 3) visible asynchronies or suspected intrinsic PEEP	1) contraindication to nasogastric tube placement 2) poor short-term prognosis or "Do not resuscitate" order already established and in palliative care.
Demoule (2016)[109]	1) Received endotracheal mechanical ventilation for > 24 h for ARF of respiratory causes 2) Ability to sustain PSV for at least 30 min with a total level of inspiratory pressure below 30 cmH2O, estimated remaining duration of IMV >48 h,	1) Age < 18 years 2) known pregnancy 3) participation in another trial within the 30 days preceding completion of the eligibility criteria, 4)Contraindication to placement of the NAVA oesophageal tube (i.e. any contraindication to placement of a gastric tube or repositioning of a tube already in place, recent gastrointestinal suture, rupture of oesophageal varices with gastrointestinal bleeding during the 4 days prior to inclusion)

Study	Inclusion criteria	Exclusion criteria
	3) level of sedation at most 4 on the Ramsay scale in the absence of medical decision to increase the level of sedation, 4) FiO2 ≤50 % with PEEPe ≤8 cmH2O 5) Not required of high-dose vasopressor therapy defined as norepinephrine above 0.3 μg kg−1 min−1 or dopamine above 10 μg kg−1 min	5)decision to withhold life-sustaining treatment.
Di mussi (2016)[10]	1)≥ 18 years old, orotracheally or nasotracheal intubated had been ventilated for acute respiratory failure with CMV (flow-limited, pressure-limited or volume-targeted pressure-limited) for ≥72 hours consecutively and were candidates for assisted ventilation. 2) Required PEEPe ≤10cmH2O, FiO2<0.5, RASS between -1 3) No to moderate levels of sedation and, d) ability to trigger the ventilator, i.e., to decrease pressure airway opening (PAO) >3–4 cmH2O during a brief (5–10 s) end-expiratory occlusion test. 4) Hemodynamic stability without vasopressor or inotropes (excluding a dobutamine and dopamine infusion <5 mcg/Kg/min and 3 mcg/ Kg/min, respectively) 5) Normothermia	1) Affected by neurological or neuromuscular pathology and/or known phrenic nerve dysfunction 2) Contraindication to the insertion of a nasogastric tube (recent upper gastrointestinal surgery, oesophageal varices).
Carteaux (2016)[46]	1)Has the ability to trigger every ventilatory cycle 2) Richmond Agitation Sedation Scale ≥–3, 3)SpO_2 ≥90% with FIO_2 ≤0.6 and PEEPe ≤ 8 cm H_2O 4) Temperature between 36°C and 39°C No patient received any sedative drug during the study.	1) Contraindication to oesophageal catheter insertion 2) Severe cardiac arrhythmia with heart rate more than 130/min, epinephrine or norepinephrine infusion more than 0.3 μg/kg/min, 3) Age <18 years, pregnancy, or moribund patient.
Doorduin (2015)[151]	Adult patients who fulfilled the Berlin definition of ARDS.	1)Patients who had hemodynamic instability. 2)Contraindications to changing a nasogastric tube (*i.e.*, recent nasal bleeding, upper airway/oesophageal pathology, or surgery) 3) Previously known neuromuscular disorder
Liu (2015)[140]	1) Static PEEPi ≥5 cmH_2O 2) Hemodynamic stability (heart rate<140 beats/minute, no vasopressors required, or <5 μg/ kg/min dopamine); 3) No sedation or minimal analgesia with low dose of morphine (<3 mg/h, by continuous	1)Tracheostomy 2)Treatment abandonment 3) History of oesophageal varices 4)Gastroesophageal surgery in the previous 12 months or gastroesophageal bleeding in the previous 30 days 5) Coagulation disorders (international normalized ratio >1.5

Study	Inclusion criteria	Exclusion criteria
	intravenous infusion 4) breathing spontaneously but in need of partial ventilatory assistance, and 5) Awake and able to positively cooperate, defined as the ability to follow an instruction	and activated partial thromboplastin time >44 s) 6) History of acute central or peripheral nervous system disorder or neuromuscular disease, and 7) Lack of informed consent.
Yonis (2015)[20]	1)Ventilated IMV and present with predictive criteria of difficult weaning 2) Difficult weaning was defined as a high duration of mechanical ventilation, or a history of respiratory (chronic obstructive pulmonary disease and restrictive disease), heart (left heart failure and coronary artery disease) or neuromuscular diseases. 3) Stop sedation 4) Meet the consensus for weaning criteria[175]	1) Contraindication to Edi catheter placement (e.g., recent gastric or oesophageal surgery and the presence of oesophageal varicose veins) 2) presence of a tracheotomy 3) a progressive infectious process, such as nosocomial pneumonia, which was defined with at least two of the following criteria: rectal temperature > 38.5 °C or < 36.5 °C, mucopurulent bronchial secretions, recent or persistent diffuse or localized parenchymatous infiltrate on pulmonary X-ray, and hyperleukocytosis greater than 12 G/L or leukopenia less than 5 G/L, associated with a positive bacteriological swab obtained by bronchoalveolar washing (positive if ≥ 104 CFU/ml) or by tracheal aspiration (positive if ≥ 106 CFU/ml); nosocomial bacteraemia, defined in accordance with the Bone criteria for a septic syndrome; hemodynamic failure with a mean arterial pressure < 65 mmHg or a need for catecholaminergic treatment 4) Decision to withhold life-sustaining treatment and presence of a guardianship.
Schmidt (2015)[149]	1) Ventilated for acute respiratory failure via an endotracheal tube for > 48 hour 2) Have the ability to trigger the ventilator with an FiO2 of ≤0.5 and PEEPe ≤5 cmH2O) 3) sedation had been stopped for more than 6 hours, 4) hemodynamic stability was achieved without vasopressor or inotropic medication.	1) known or suspected phrenic nerve dysfunction or other neuromuscular disorders that may involve the diaphragm or impair respiratory drive. 2) Contraindications to Edi catheter placement 3) Patients in whom the decision had been made to withhold life-sustaining treatment
Vaschetto (2014)[152]	1) intubated patients with central venous and arterial indwelling catheters undergoing partial ventilatory support for ≤ 48 hours 2) Received only short-acting sedative agents (i.e., Propofol and/or Remifentanil), and with a Glasgow Coma Scale greater than 10 at sedation discontinuation. Criteria for protocol discontinuation 1)hemodynamic instability as defined in exclusion criteria	1) Age ≤18 years 2) contraindications for an electrical activity of the Edi catheter placement, i.e., oesophageal varices, upper gastroesophageal bleeding in the previous 30 days, and gastroesophageal surgery in the previous 12 months 3) hemodynamic instability despite adequate filling (i.e., need for epinephrine or vasopressin infusion, or need for dopamine or dobutamine> 5 µg/kg/min, or need for

Study	Inclusion criteria	Exclusion criteria
	2) agitation 3) Inability to maintain pulse arterial oxygen saturation ≥92%.	norepinephrine > 0.1 µg/kg/min to maintain mean arterial blood pressure > 60 mm Hg); 4) core temperature > 38°C, 5); renal failure (i.e., blood creatinine ≥ 110 µmol/L); 6) pregnancy 7) presence of major painful stimuli, such as recent surgical wound or traumatic injuries 8) history of allergy to Propofol components 9) Inability to maintain a V_T ≤ 8 mL/kg with a minimum inspiratory support of 8 cm H_2O 10) PEEPe > 12 cm H_2O and/or FIO_2 > 0.6 11) Prior Propofol infusion > 2 mg/kg/h lasting 8 hours or more or < 2 mg/kg/h for < 8 hours whenever Propofol washout was not possible because of occurrence of either agitation, as defined RSS or hypertension (arterial systolic pressure > 180 mm Hg) and tachycardia (> 125 bpm), or unbearable patient's discomfort; and 12) inclusion in other research protocols.
Mauri (2014)[16]	1)ARDS patients with low Cstrs values (as reported by the attending physician) undergoing ECMO within 48 h after switching from controlled ventilation to PSV	1)Age <18 years 2)Hemodynamic instability 3) contraindications to inserting a NAVA dedicated nasogastric tube (NGT) (e.g., nasal bleeding)
Patroniti (2012)[147]	1)Patients with ARF receiving partial ventilatory support Study protocol	1) Age< 18 years 2) Contraindication to nasogastric tube positioning or substitution (gastroesophageal surgery in the previous 12 months, gastroesophageal bleeding in the previous 30 days, history of oesophageal varices, facial trauma, and/ or surgery), hemodynamic instability 3) Unavailability of the Servo-I ventilator integrating the NAVA module
Piquilloud (2011)[1]	1)intubated for acute respiratory failure and ventilated with PSV	1) Age ≤ 16 years 2)Hypoxic required FiO_2 ≥ 0.5 3) Haemodynamic instability 4)Oesophageal problem, active upper gastro intestinal bleeding 5) Contraindication for naso-gastric tube insertion 6) High risk of death in the next 7 days and have neuromuscular disease
Spahija (2010)[65]	1)Ready for ventilator weaning and fulfilled established weaning criteria	No exclusion criteria were set.

Study	Inclusion criteria	Exclusion criteria
	2) All continuous sedative infusions were discontinued at least 4 hours before starting the trial.	
Terzi (2010)[2]	1) ARDS patients caused by pulmonary disease ventilated with IMV and able to breathing spontaneously and pneumatically triggering the ventilator for 24 hrs. 2) required PS ≤ 20 cm H2O 3) Definition of ARDS based on four criteria as per The American European Consensus Conference on ARDS.[176]	1) Age < 18 years 2) Hemodynamic instability or a history of oesophageal varices or gastroesophageal bleeding in the past 30 days. 3) Requiring sedation received Propofol only, without opiates, to maintain the RSS score 2 to 3
Colombo (2008)[22]	All intubated patients receiving partial ventilatory support	1) Age 18 years 2) Gastro-oesophageal surgery in the previous 12 months 3) Gastro-oesophageal bleeding in the previous 30 days 4) History of oesophageal varices and facial trauma and/or surgery 5) Hemodynamic instability despite adequate filling [i.e. need for continuous infusion of epinephrine or vasopressin, or dopamine >5 c/ (kg min) or norepinephrine >0.1 c/ (kg min) to maintain systolic arterial blood pressure>90 mmHg] 6) Core temperature >38 C 7) Coagulation disorders (INR ratio >1.5 and PTT >44 s), 8) Inability to maintain a tidal volume≤8 ml/kg with a minimum inspiratory support of 8 cmH2O 9) Inclusion in other research protocol.

Appendix X: Description of statistical analysis perform in included studies

Statistical Test	Description	Statistical analysis used in study
Kolmogorov–Smirnov test	The Kolmogorov-Smirnov test is used to check the assumption of normality.[145,153]	**Costa 2017[148]** **Schmidt2015[149]** **Yonis 2016[20]** **Piquilloud 2011[1]**

Statistical Test	Description	Statistical analysis used in study
Shapiro-Wilks test	The Shapiro-Wilks test is the test for normality distribution data. It provides a more specialized alternative to the Kolmogorov-Smirnov test. This test compares the variance of the data, estimated with the variance expected by normal distribution.	**Patroniti 2012[147]** The normality assumption was tested by the Shapiro–Wilks test. The AI% data were reported in median and IQR, which assumed the data are not normally distributed. Continuous data (AI%) and categorical variable (AI>10%) were not statistically analysis.
D' Angostino test	D' Angostino test is one of the main test of normality assumption test, which it recommended to used additional to the graphical assessment of normality. [146]	**Di mussi 2016[10]** All data were test for normality distribution, Data of AI% was non-parametric as was reported in median and IQR.
Analysis of Variance (ANOVA)	Analysis of variance is a nonspecific null hypothesis (Ho) test for normally distributed data, and when Ho is rejected, the conclusion is that at least one population mean is different from at least one other means, so the post hoc analysis is needed. An ANOVA is conducted in one factor (independent variables) is called a one-way ANOVA and in two factors, then the ANOVA is called a two-way ANOVA.[153,158] One-way ANOVA with repeated measures is used to compare three or more group means where the participants are the same in each group. This usually occurs in two situations: 1. when participants are measured multiple times to see changes to an intervention. 2. when participants are subjected to more than one condition/trial and the response to each of these conditions wants to be compared.[158] A two-way repeated measures ANOVA is used to compare the mean differences between groups that have been split on two within-subjects' factors to evaluate if there is an interaction between these factors on the dependent variable. A two-way repeated measures ANOVA is often used in studies where a dependent variable is measured over two or more-time points, or when subjects have undergone two or more conditions.[153]	**Doordin 2015[151]** One-way ANOVA for repeated measures was performed to compare modes. **Mauri 2013[16]** Two-way ANOVA for repeated measures with study phase as within-subject and randomization sequence as between-subject factors (modes, ETS and AI%) was used. **Terzi 2010[2]** The two-way ANOVA was used to test for each variable dataset. When two-way ANOVA identified a significant interaction, mixed-model analysis was performed to evaluate the effects of assist level by ventilation mode, **Spahija 2010[65]** Variables were compared between NAVA and PSV and the two levels of assist, using two-way repeated-measures ANOVA.

Statistical Test	Description	Statistical analysis used in study
Friedman test	The Friedman test is a non-parametric alternative to the one way ANOVA with repeated measures and used to test for differences between groups for a matched datasets.[153,177]	**Beloncle 2017[21]** The measured parameters were compared across the different steps using nonparametric Friedman test. **Doorduin 2017[151]** Friedman Test was used as the data are nonparametric equivalent to compare difference between the modes. **Carteaux 2016[46]** The effect of the level of assistance during NAVA and PSV was assessed separately by a Friedman test. **Liu 2015[140]** The effects of PEEPe levels were assessed within the mode, within both modes and between PSN(NAVA) PEEPe 0% and PSP(PSV) PEEPe80%. The datasets were non-parametric, the data then analyzed within-subject comparison of all eight conditions with one-way repeated measures ANOVA on ranks was used. **Schmidt 2015[149]** Friedman ANOVA for repeated measures was performed to compare the prevalence of the main asynchronies between three modes as data failed normality test **Vaschetto 2014[152]** Friedman tests for repeated-measures analysis of variance by ranks was used because of a small sample size and nonparametric data. It was used to compare continuous variables which compared between depths of sedation within each ventilatory mode.
Mixed models	Mixed model is a data analysis that used of both random and fixed effects. It is a flexible approach to corelated data included repeated measures on each subject overtime, or to multiple related outcome measures at one point in time.[178]	**Terzi 2010** The mixed model analysis was used to evaluate the modes affect the level of assist.
The Wilcoxon signed rank test	Sign test or Wilcoxon test is used to compare two repeated measures is a nonparametric alternative to the paired t-test. The data needs to meet four assumptions: 1. Dependent variable should be measured at the ordinal or continuous level 2. Independent variable should consist of two categorical independent groups.	**Ferreira 2017[24]** The paired Wilcoxon signed-rank test was used to compare continuous variables during the SBT in NAVA and PSV. **Beloncle 2017[21]** The measured parameters were compared across the different steps (factors) Wilcoxon tests were used to perform *post hoc* pairwise comparisons with correction for multiple comparisons using the false discovery rate approach. **Carteaux 2015[46]**

Statistical Test	Description	Statistical analysis used in study
	3. Have independence of observations (data taken from the same group or two separate occasions or data from matched group) 4. Two variables are not normally distributed.[157,177]	The effect of the level of assistance during NAVA and PSV was assessed separately by a Friedman test and then a Wilcoxon test. **Yonis 2016[20]** The two modes of ventilatory support were compared using the non-parametric Wilcoxon test the groups was performed by the χ^2 tests. **Vaschetto 2014[152]** Pairwise comparisons test was performed with the Wilcoxon test.
Mann-Whitney U test	Mann-Whitney U test is sometimes called Wilcoxon Mann Whitney U test. It is used to compare two separates unrelated (independent) groups and is a non-parametric alternative to a two-sample t-test, or any distribution data provide there is reasonable spread of data across the range.	**Demoule 2016[109]** Differences between groups were assessed with The Mann–Whitney U test for continuous variables. **Di mussi 2016[10]** The breathing parameters data is not normally distributed. The Mann-Whitney U test was used to compare AI% (continuous data) between two modes. Mortality outcome was not statistically analyzed.
Student– Newman–Keuls test	The Newman-Keuls method is used to perform pair wise comparisons and a stepwise approach, comparing pairs ordered from smallest to largest. It considers separately the alpha of each of the possible contrasts.[158]	**Liu 2015[140]** Student-Newman-Keuls test for *post hoc* analysis of multiple comparisons was used following the one-way repeated measures ANOVA on ranks was used (within subject of eight conditions). It used to identify the difference of effects of PEEPe levels within the mode, within both modes and between PS_N(NAVA) PEEPe 0% and PS_P(PSV) PEEPe80%. **Piquilloud 2011[1]** A *post hoc* pairwise comparisons were performed using the Newman–Keuls procedure. **Spahija2010[65]** The Student-Newman-Keuls test was used for *post hoc* test to identify significant effects.
Dunn's test	Dunn's test is a multiple non-parametric pairwise test following rejection of a Kruskal-Willis test, for control of family wise error rate, and the false discovery rate.[179]	**Doordin 2015[151]** *Post hoc* analysis was performed with the Student– Newman–Keuls test or Dunn test.
McNemar's test	The McNemar's test is used to determine if there are differences on a dichotomous dependent variable between two related groups (paired data).[153]	**Costa 2017[148]** The asynchrony index (categorical) was compared by McNemar's test and a *P* value< 0.05 was considered significant.

Statistical Test	Description	Statistical analysis used in study
The χ^2 tests	The χ^2 tests are used with any number of variables to determine an association in between two categorical variables in the sample are likely to reflect a real association between these two variables in the population. They are a non-directional hypothesis test. To use the χ^2 tests four assumptions must be satisfied in general. 1. Samples are independent 2. Participant in each group have been randomly and independent selected. 3. The classification categories in the distribution are mutually exclusive and exhaustive. The sample size is reasonably large.[150]	**Demoule 2016[109]** The was used to evaluate categorical variables, which is mortality outcomes (as number of events and percentage).
Yate's correction	The effect of Yates' correction is used to prevent overestimation of statistical significance for small data. It might be applied to a χ^2 analysis when evaluating the association between two dichotomous variables.[159]	**Yonis2016[20]** Yates correction was used when necessary after the two modes of ventilatory support were compared by using the non-parametric Wilcoxon test then the groups was performed by the χ^2 tests.
Fisher's exact test	Fisher's exact test is used to evaluate an association and difference in two categorical variables, where the outcomes can be classified as either present or absent for example. It is a non-parametric test when using the χ^2 test assumptions are not satisfied.[153,157]	**Colombo 2008[22]** Asynchrony index >10% was compared between the two modes using Fisher's exact test. **Vaschetto 2014[152]** Categorical data were compared by Fisher exact test.
The Tukey Test	The Tukey Test or Tukey procedure or Tukey's Honest Significant Difference test, is a post-hoc test for multiple comparisons to identify where those differences lie. The test compares all possible pairs of means to keep error rates low.[158]	**Mauri 2014[16]** Tukey method was used if the ventilation strategy effect was statistically significant, a post hoc analysis was performed comparing the three treatments at each step.
Benjamini-Hochberg	Benjamini-Hochberg is used to control the false discovery rate provided the test statistics have a certain positive regression dependency.[160]	**Carteaux 2016[48]** Benjamini-Hochberg correction was used for paired measures.
Bonferroni adjustment/ Correction	Bonferroni post-test is for multiple comparisons and used to control the familywise error rate. It is used to correct a	**Doordin 2015[151]** Bonferroni post-test was performed to test for associations, a two-tailed $P < 0.0001$ was considered significance for comparing the NeuroSync index between three modes. **Patroniti 2012[147]**

Statistical Test	Description	Statistical analysis used in study
	critical *P* level for significance, the alpha then set in a lower critical value. It adjusts for number of tests.[157,180]	Bonferroni correction was used to compare each level of assistance with both the highest and lowest level of assistance within the same ventilatory mode. **Vaschetto 2014[152]** Bonferroni correction was used for adjusting the threshold for statistical significance by means of for multiple comparisons; *p* values less than 0.017 were considered significant.

Appendix XI: Outcome data extraction and calculation

Asynchrony index (%)

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV		Calculated *p* value	*p* value
	Total	Withdraw	Mean	SD	Mean	SD		
Beloncle 2017[21]	11	0	1.33*	2.96*	0.83*	1.11*	0.605	NR
Ferreira 2017[24]	20	0	11.8*	11.49*	21.7*	20.9*		0.033
Di mussi 2016[10]	NAVA:20 PSV:18	NAVA:7 PSV:6	5.84*	3.4*	12.53*	11.38*		0.04
Demoule 2016[109]	NAVA:62 PSV:66	NAVA:9 PSV: 16	16.23*	6.97*	29.2*	21.27*	0.0001	0.001
Carteaux 2016[46]	11	0	0.23*	0.52*	0*	0*	0.16	>0.05
Yonis 2015[20]	30	0	7.32*	14.65*	12.61*	25.55*	0.0015	0.0015
Schmidt 2015[149]	16	0	1.6*	1.72*	0.64*	0.92*	0.06	>0.05
Vaschetto 2014[152]	16	2	0	0	7.6	NR	0.0001	NR

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV		Calculated *p* value	*p* value
	Total	Withdraw	Mean	SD	Mean	SD		
Mauri 2013[16]	10	0	20	13	74	43	0.01	0.01
Patroniti 2012[147]	15	1	0	0	1.667*	3.704*	0.116	NR
Piquilloud 2011[1]	25	3	5.67*	5.41*	14.4*	16.01*	0.019	<0.05
Terzi 2010[2]	11	0	1.5 ¥	1 ¥	4.5 ¥	1 ¥	0.0001	NR
Colombo 2008	16	2	0*#	0*#	7.1*#	14.77*#	0.073	NR

Asynchrony index > 10%

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV	
	Recruit sample	Withdraw	Number of events	Total sample size	Number of events	Total sample size
Ferreira 2017[24]	20	0	12	20	11	20
Costa 2017[148]	13	0	0*	13	5*	13
Beloncle 2017[21]	11	0	1	11	0	11
Carteaux 2016[46]	11	0	1	11	0	11
Yonis 2015[20]	30	0	5	30	9	30
Schmidt 2015[149]	16	0	0	16	0	16
Vaschetto 2012[152]	16	2	0	14	2	14
Patroniti 2012[147]	15	1	0	14	4	14

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV	
	Recruit sample	Withdraw	Number of events	Total sample size	Number of events	Total sample size
Piquilloud 2011[1]	25	3	6	22	12	22
Colombo 2008[22]	16	2	0*	14	3*	14

NeuroSync index

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV		Calculated *p* value	*P* value
	Total	Withdraw	Mean	SD	Mean	SD		
Doorduin 2015[151]	12	0	(7.673)#	(4.331)#	(21.23)#	(21.076)#	0.04	<0.05*
Liu 2015[140]	12	0	6.6	2.52	19.7	15.12	0.007	

Patient ventilator asynchrony percentage

Study name	Sample size	Factors of study	Intervention outcome: NAVA		Comparator outcome: PSV		Calculated *p* value	*P* value
	Total		Mean	SD	Mean	SD		
Spahija 2010[65]	14	(NAVA-low vs PSV-low)	7	2	18	3	0.0001	NR
		NAVA-high vs PSV-high	7	2	23	12	0.0001	NR

Mortality in intensive care unit

Study name	Sample size		Intervention outcome: NAVA		Comparator outcome: PSV	
	Recruit sample	Withdraw	Number of event	Total sample size	Number of events	Total sample size
Di mussi 2016[10]	NAVA: 62 PSV:66	0	8	66	14	66
Demoule 2016[109]	NAVA:20 PSV:18	NAVA:7 PSV:6	0	13	3	12

#: Data provided by the primary authors; ¥: Estimated from figure; NR: not report,*: Calculated data (Mean and SD) used MedCalc software. This procedure calculates the difference of an observed mean with a hypothesized value. A significance value (*p* value) and 95% confidence interval (CI) of the observed mean is reported. The *p* value is the probability of obtaining the observed mean in the sample if the null hypothesis value were the true value. The *p* value is calculated using the one sample *t*-test, with the value *t* calculated as:

$$t = \frac{sample\ mean\ -\ hypothesized\ mean}{standard\ error\ of\ sample\ mean}$$