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Neurally adjusted ventilator assist (NAVA) in infants with acute respiratory failure: a literature scoping review

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The authors have nothing to disclose.

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JH, RE, ST, JML contributed to the development of the review protocol. JH and JML contributed to the data selection and data extraction. JH, RE, ST, JML contributed to the data synthesis. JH and JML wrote the first draft of the manuscript; all authors contributed to revision and accepted the final manuscript.

Article Tweet (max 140 characters):

NAVA efficacy and benefit on sedation practice remains unclear in infants with acute respiratory failure

#PedsICU @julesharris2 @JosLatour1 @rdepu

ABSTRACT

Objective: To map the evidence for neurally adjusted ventilatory assist (NAVA) strategies, outcome measures, and sedation practices in infants <12 months with acute respiratory failure (ARF) using the PRISMA Extension for Scoping Reviews guidance.

Data sources: CINAHL, MEDLINE, COCHRANE, JBI, EMBASE, PsycINFO, Google scholar, BNI, AMED. Trial registers included: Clinical trials.gov, EU clinical trials register, ISRCTN register. Also included were: Ethos, grey literature, Google, dissertation abstracts, EMBASE conference proceedings.

Study selection: Abstracts were screened followed by review of full text. Articles incorporating a heterogeneous population of both infants and older children were assessed, and where possible, data for infants were extracted. Fifteen articles were included. Ten articles were primary research: Randomized controlled trial (RCT) (n=3), cohort studies (n=4), retrospective data analysis (n=2), case series (n=1). Other articles: expert opinion (n=2), NAVA updates (n=1) and a literature review (n=2). Three studies included exclusively infants. We also included 12 studies reporting jointly on infants and children.

Data extraction: A standardized data extraction tool was used.

Data Synthesis: Key findings were that evidence related to NAVA ventilation strategies in infants and related to specific primary conditions is limited. The Setting of NAVA level is not consistent and how to optimize this mode of ventilation was not documented. Outcome measures varied considerably, most studies focused on improvements in respiratory and physiological parameters. Sedation use is variable with regards to medication type and dose. There is an indication that less sedation is required in patients receiving NAVA, but no conclusive evidence to support this.

Conclusions: This review highlights a lack of standardized strategies for NAVA ventilation and sedation practices among infants with ARF. Studies were limited by small sample sizes and a lack of focus on specific patient groups. Robust studies are needed to provide evidence-based clinical recommendations for the use of NAVA in infants with ARF.

Key words: Neurally Adjusted Ventilatory Assist; Mechanical ventilation; Respiratory Therapy; Acute Respiratory Failure; Bronchiolitis; Infants.

INTRODUCTION

Report in Context

- To date, there is a lack of standardization in ventilation strategies for infants with Acute Respiratory Failure (ARF).
- Neurally Adjusted Ventilatory Assist (NAVA) is a ventilator mode increasingly used in infants, which offers several theoretical benefits, such as improved patient-ventilator synchrony.
- This scoping review maps NAVA use in infants, examining utilization techniques, sedation strategies and outcome measures.

Between 2016-2018, 60,260 children were admitted to Pediatric Intensive Care Units (PICUs) in the United Kingdom. Infants less than one year of age with a primary respiratory diagnosis accounted for 17,936 of these admissions (1,2). Previous studies highlighted a lack of standardization in terms of the therapeutic approach to infants with acute respiratory failure (ARF), resulting in variations in resource utilization and outcome (3-5). Recently, published recommendations for mechanical ventilation of children and neonates (PEMVECC) have provided guidance on ventilation modalities and physiological targets; however, the authors were unable to make firm recommendations across a wide spectrum of pathologies (6). Of note, the authors stated: “Ventilator mode should be dictated by clinical experience and theoretical arguments, considering the pathophysiology of the disease” (6). Provision of effective mechanical ventilation can be challenging for infants with ARF and may carry side effects (7). A variety of reasons specific to infants contribute to this; immature receptors and controllers of breathing, small airways, air trapping, and mucus plugging (8).

Conventional modes can cause ventilator insufficiency in infants with ARF for three reasons: asynchrony, intrinsic positive end expiratory pressure (PEEP), often high in the infant with respiratory failure, and increased use of sedating medication

(8). Infants have an intact Hering–Breuer reflex which conventional modes of mechanical ventilation can elicit. This results in a prolonged expiration or interrupted inspiratory time (9). Conventional modes are often associated with patient-ventilator asynchrony (9,10,11,12), requiring the use of heavy sedation and sometimes muscle relaxants (13,14). Patient ventilator asynchrony demonstrates a contribution to increased respiratory drive and increased loading of the respiratory muscles (15,16), this is further compounded by intrinsic PEEP in those infants with obstructed peripheral airways in respiratory illnesses such as bronchiolitis (8).

A recently developed mode of ventilation, Neurally Adjusted Ventilatory Assist (NAVA), was first discussed by Sinderby et al in 1999 (17). NAVA provides pressure support in proportion to the patient's diaphragmatic electrical activity (Edi), thereby individualizing support to the patient's neural drive. Because this is activated early within the respiratory cycle, improved synchrony is achieved. In theory this allows the patient to be ventilated at lower pressures and volumes and, therefore, minimizes the risks of lung trauma (18). There are several studies indicating that NAVA decreases asynchrony and is safe (11,19,20,21,22). However, there are also several disadvantages of NAVA, including: lack of availability across all ventilator models, need to site a nasogastric tube (although this can also be used for feeding), and potential for suboptimal placement resulting in an inaccurate Edi estimation.

Standard modes of ventilation achieve apparent synchrony in infants with ARF using high doses of sedatives and, occasionally, muscle relaxants, potentially prolonging length of ventilation days and hospital stay (23,24). Consequences of prolonged periods of sedation with or without muscle relaxants are muscle wastage, including the respiratory muscles, increased risk of secondary infections, and potential for withdrawal or delirium (25,26).

The aim of this scoping review is to examine and map the use of invasive NAVA in infants up to one year of age with ARF and to explore the sedation strategies. The scoping review questions were: 1. What strategies are described in the use of invasive NAVA in infants with ARF? 2.What outcome measures are used to assess the effectiveness of invasive NAVA? 3. What sedation practices are described when infants with ARF receive invasive NAVA?

MATERIALS AND METHODS

This scoping review utilises the framework by Arksey and O'Malley (27) and is structured and reported according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) (28). Arksey and O'Malley identify four types of scoping review. This scoping review focuses on examining the extent, range and nature of research activity. This type of scoping review does not aim to describe findings in detail but to map data findings and identify gaps in knowledge (27).

Eligibility Criteria

Inclusion criteria: Infants > 36 weeks gestation and < 1 year or papers that included all children if this age range was represented; Infants with ARF; Infants requiring NAVA via endotracheal tube; Infants admitted to PICU. For the purposes of this review ARF is defined as patients who are unable to maintain adequate gas exchange; acute refers to respiratory failure commencing <48 hours before mechanical ventilation. Papers were included if they described a population of infants and children. Papers were excluded if they included only adults or only pre-term infants < 36 weeks or discussed non-invasive NAVA strategies.

The search was not limited by publication year, country or methodology. Articles were limited to those in the English language. All published and unpublished studies, related articles, and conference abstracts were considered for review.

Information sources and Search

The search strategy included the following databases: CINAHL, MEDLINE (Electronic Supplement Material 1), COCHRANE, JBI, EMBASE, PsycINFO, Google Scholar, BNI, AMED. Trial registers searched included: Clinical trials.gov, EU clinical trials register, ISRCTN register. The search for unpublished studies included: Ethos, grey literature, Google, dissertation abstracts, EMBASE conference proceedings. The search included all studies up to 16th June 2020.

Selection of sources of evidence

A search of databases and hand sift was performed. Titles and abstracts were reviewed. Full text articles were reviewed by two reviewers (JH, JML). During the search it was noted that very few articles exclusively included infants with ARF, studies tended to include the entire PICU population. Therefore, the decision was made to include articles if they included infants with ARF, and where possible the data for these infants could be extracted.

Data charting process and data items

Data were extracted using a standardized data extraction tool (29) by two independent reviewers (JH, JML). Disagreements that occurred between reviewers were resolved through discussion or with a third reviewer (RE). A charting table was developed and trialed on the first three studies to ensure all relevant data was extracted and changes made where appropriate.

Critical appraisal of individual sources of evidence

As stated by the Arksey and O'Malley (27) guidance for scoping reviews, quality assessment of the evidence is not required and was thus not performed.

Synthesis of results

Included articles were synthesized via three main themes: NAVA ventilation strategies, NAVA ventilation effectiveness, and sedation practice in infants receiving NAVA.

RESULTS

Thirty-nine full text articles were reviewed following title and abstract review of 149 articles. Twenty-four of these were excluded with reasons shown in **Fig.1**. Finally, 15 articles were included (Table 1 - Digital Supplement). Ten articles were primary research including three RCT's, four cohort studies, two retrospective data analysis studies and one case study. The remaining five articles were reviews (n=3) and expert opinion (n=2). Primary outcome measures of the research articles are presented in **Table 1**. Sample size ranged from three to 170 infants/children. Of the ten research articles, three included infants less than one year exclusively, one included infants 0-24 months and six included children up to 16 years. Four studies focused on respiratory illness and six studies included all PICU diagnosis; the proportion of infants and primary diagnosis of the studies are presented in **Table 2**.

NAVA ventilation strategies

Information regarding ventilation strategies with NAVA was limited; the focus being how NAVA was used i.e. weaning, initial setting of NAVA level, duration of ventilation and measures to prevent lung injury (**Table 2-Digital supplement**). Studies used NAVA as an initial mode of ventilation (22,30-34) or as a weaning mode of ventilation (21,35), two studies did not specify a time point that NAVA was initiated (36,37).

In five studies, initial NAVA level was set to reflect the peak inspiratory pressure (PIP) in the previous mode of ventilation (22,30,31,32,35). Piastra et al set NAVA level to achieve tidal volumes of 6mls/kg, whilst Clement et al had set NAVA level to achieve the same Tidal Volumes (TVs) as the conventional mode the patient was on (21,35). Two studies reported that they used a NAVA level of 1.0 cm/microvolt to maintain the Edi between 5-15 microvolts (30,34). In Kallio's study, NAVA levels at the beginning of ventilation were significantly higher (p0.04) in patients with ARF, than those without underlying lung pathology (31). This is not surprising given the restrictive or obstructive nature of conditions that lead to acute respiratory failure.

Two studies set the peak inspiratory pressure alarm to 35cm$H_2$0 to prevent lung injury (31,32). An update published by Sinderby and Beck described that acute lung injury in patients <1year resulted in a high Edi signal during exhalation in the absence of PEEP, increasing PEEP in these patients reduced this (38).

Measures of NAVA ventilation effectiveness

Measures of NAVA effectiveness included physiological variables, patient ventilator interaction, respiratory variability, and work of breathing (**Table 3-digital supplement**). Several studies used physiological variables as a measure of effectiveness (21,22,30,35,35). Bourdessoule et al observed little change in SPO_2, End tidal CO_2, heart rate, PEEP, Fraction of inspired oxygen, tidal volumes or mean and peak ventilator pressures (36). Conversely, other studies observed a reduction in mean airway pressure (33,35,36) and PIP (21,30,33,35). A case study of three children, two of which had bronchiolitis less than 1 year old, showed a decrease in FiO_2 and PIP (34). However, there were no observed differences in other physiological variables between NAVA and PSV or PCV except for Piastra et al who noted an increase in respiratory rate in 10 infants with Acute Respiratory Distress Syndrome (35). De la Oliva et al observed breath-to-breath variability which was found to be significantly increased (p=0.0125) in patients on NAVA compared to PSV (22). Kallio et al echoed this, finding patients receiving NAVA had increased respiratory rate and decreased tidal volumes when compared to conventional modes (31). Baudin et al (37) noted variability within the Edi trace on NAVA comparable to that of spontaneously breathing infants, whereas PSV and PCV showed a decrease in variability with this being significant in the PCV versus NAVA group (P 0.013).

Four research articles demonstrated an improvement in patient-ventilator interaction achieved by measuring the asynchrony index (21,22,33,36). The included expert opinion articles also agreed with this observation (39,40,41,42). Bourdessoule et al demonstrated, by observing shorter trigger delays, lower percentage of wasted efforts and an overall lower accumulated asynchrony index; trigger delay was reduced in NAVA (15%) compared to PSV (23%) and PCV (25%) (36). The authors also reported a significant early cycling off or initiation of a breath in PCV (12%) and PSV (25%) compared to NAVA (0.3%). However, only one patient received PSV in this study (30). A decrease in trigger delay and ventilator response time in NAVA when compared to PSV exclusively was also reported (21). This finding was echoed by De la Oliva et al, who observed less asynchrony in NAVA, this study used Edi to calculate trigger delay providing more accurate data than the use of flow curves as used by Clement et al (21,22).

Two methods of assessing work of breathing were identified in the included articles: Pressure Time Product (PTP) and Edi (21,33). PTP was calculated by measuring the waveforms at the initiation of breath to ventilator pressurization (trigger delay) and the point of ventilator pressurization and return to baseline (response time). This demonstrated a reduced trigger delay and response time with the authors suggesting that this indicated a decrease in work of breathing (21). The method of PTP has not been used in other pediatric studies. Alander et al used Edi as a trigger for patient breathing rather than pressure curves as Edi reflects the electrical activity of the diaphragm and is therefore a more accurate marker of initiation of breathing (33). Clement et al did not have access to Edi monitoring until half-way through their study (21).

The duration of ventilation did not differ significantly between the NAVA and control groups (p=0.07) (30). However, duration of ventilation was significantly lower in the NAVA group than the control group as reported by Piastra et al in their study evaluating NAVA versus PSV following high frequency oscillatory ventilation (HFOV) (35). In this study it is worth noting that patients receiving NAVA had spent a significantly longer duration on HFOV. Kallio et al's study showed a longer duration of ventilation of 30.4 hours (median) in the group with ARF when compared to those with healthy lungs at 2.1 hours (median) (31).

Sedation practice in infants receiving NAVA

Most studies did not titrate sedation as part of the study protocol (**Table 4- digital supplement**) (22,32,35). One study however, specified that physicians or nursing staff would titrate sedation using locally established clinical guidelines (36).

A range of sedatives were used in the included research articles (**Table 4- digital supplement**). In Duyndam et al's study, morphine and midazolam dosages were 5mcg/kg/hr and 178.5 mcg/kg/min respectively, with four patients not receiving any sedation (32). It is not clear whether any of these patients received bolus sedation medications at any time. The authors did not find any difference between the modes of ventilation with regards to COMFORT scores (32). The COMFORT score is a widely used, validated pain, sedation and distress assessment tool in PICU (25,43,44).

Kallio and colleagues enabled titration of sedation by the bedside team to achieve a sedation score of 4 on the Sedation Agitation Score (SAS) and with maintaining a continuous Edi trace (30). A sub-study by Kallio found that younger age and lighter sedation appeared to increase Edi, however this was not statistically significant (31). Morphine and midazolam were commonly used with the addition of ketamine and sedative boluses as required. The studies of Clement et al (21) and Duyndam et al (32), found no difference between sedation scores and sedation levels. Following a sub-analysis of the results in Kallio et al’s study it, was found that there was a significant difference (P=0.03) between the non-surgical group with the amount of sedatives used being less (31). Liet et al weaned the morphine to 8mcg/kg/hr, although there was no rationale provided for this (34).

Clement et al documented COMFORT behavioral scores, between 8-26 (21). These scores corresponded with deep to light sedation, but the authors observed no difference in comfort levels in either ventilation mode evaluated (21). Other studies observed a significant decrease in comfort levels in patients receiving NAVA, sedation level went from light sedation to deep sedation (22,34,35).

DISCUSSION

Summary of evidence

This scoping review maps the current understanding of the use of NAVA in infants and children using published research, expert opinion and review articles. The focus of the scoping review was to identify ventilation strategies when using NAVA, outcome measures, and sedation practices to map what is currently known about its clinical application in infants with ARF.

The key findings from the review are summarized in **figure 1 – digital supplement**. Although there is limited information related to the use of NAVA in infants with ARF there are some key indications that this mode of ventilation may be a more effective mode in providing synchrony with the ventilator and improving ventilatory efficiency. Asynchrony is a recognized issue with conventional ventilation modes. Several studies have demonstrated that infants and children and those with acute respiratory failure require more unique ventilation strategies to provide optimum ventilation. As an example, Kallio et al's study identified that children with ARF often had higher minimum and peak Edi and required higher PEEP levels (31), further to this there was some indication that younger age also impacted the increase in Edi. It is evident that there is still much we do not know about respiratory drive and work of breathing in this patient group. Clinicians need to understand the underlying pathology and how it responds to different modes of ventilation to effectively utilize NAVA to its optimum potential. Due to the considerable heterogeneity of the pediatric population age, diagnosis specific and in some cases age specific guidelines are required to effectively deliver this new mode of ventilation.

Sedation practice is inconclusive. To be able to initiate NAVA the diaphragm needs to be active. Further study is required to assess the levels of sedation required to ensure this signal is present. There is some indication that sedation use may be reduced in NAVA due to the decrease in asynchrony however this is inconclusive.

At the Bedside

- Evidence is lacking as to which patients may benefit from NAVA, both as a primary mode of ventilation or for weaning purposes. There is no consistent practice reported for setting NAVA level on initiation.
- Multiple outcomes are measured across all studies, including physiological and respiratory improvement, patient-ventilator synchrony, and work of breathing. No conclusive sedation strategies are described to guide clinical practice.
- There is limited evidence to demonstrate the effectiveness of NAVA in infants with ARF. Therefore, clinicians should be cautious in initiating NAVA and carefully monitor the physiological, respiratory and sedation parameters to prevent harm.

Limitations

It must be acknowledged that there is a lack of detailed assessment in this review however, this is a scoping review and therefore this detail is not required. There were ten primary studies only one of which had a large sample size of 170 infants (30). This indicates the need for more robust RCTs focusing on infants with ARF. Five of the articles were opinion papers, reviews or case studies and constitute a low level of evidence in answering the scoping review objectives reliably.

A further limitation of this review is that most studies included all the PICU population. There were two papers that specifically included infants with ARF (21,34). Unfortunately, it was not always possible to separate the results and therefore the review includes some results of children, and where the results could not be extrapolated, these children may not have a primary respiratory diagnosis. This indicates the need for further targeted studies especially with regards to the unique presentation of infants and specifically those with ARF.

CONCLUSION

This scoping review highlights the lack of robust evidence to demonstrate the effectiveness of NAVA in infants. Due to the limited sample sizes, lack of RCT's and specific patient groups under study, there is a significant gap in knowledge regarding which infants may benefit most from NAVA. As infants with ARF often have dysynchrony they may well be one of these groups that benefit. A recent NICE Medtech Innovation briefing indicated that more research with NAVA was required in specific patient groups (45). Duffet's review exploring the use of RCT's in PICU identified a lack of robust large and multi-centered RCT's in PICU's (46).

Identifying a mode of ventilation that improves synchrony and reduces the necessity of sedatives and muscle relaxants might reduce ventilator time and the associated complications of prolonged ventilation. Therefore, the next step in utilizing NAVA ventilation effectively in infants requires observational cohort studies to understand how NAVA works and how it can be applied at the bedside.

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Tables and figures

Figure 1. PRISMA flowchart of NAVA scoping review

Table 1. Primary outcome measures

Table 2. Patient characteristics

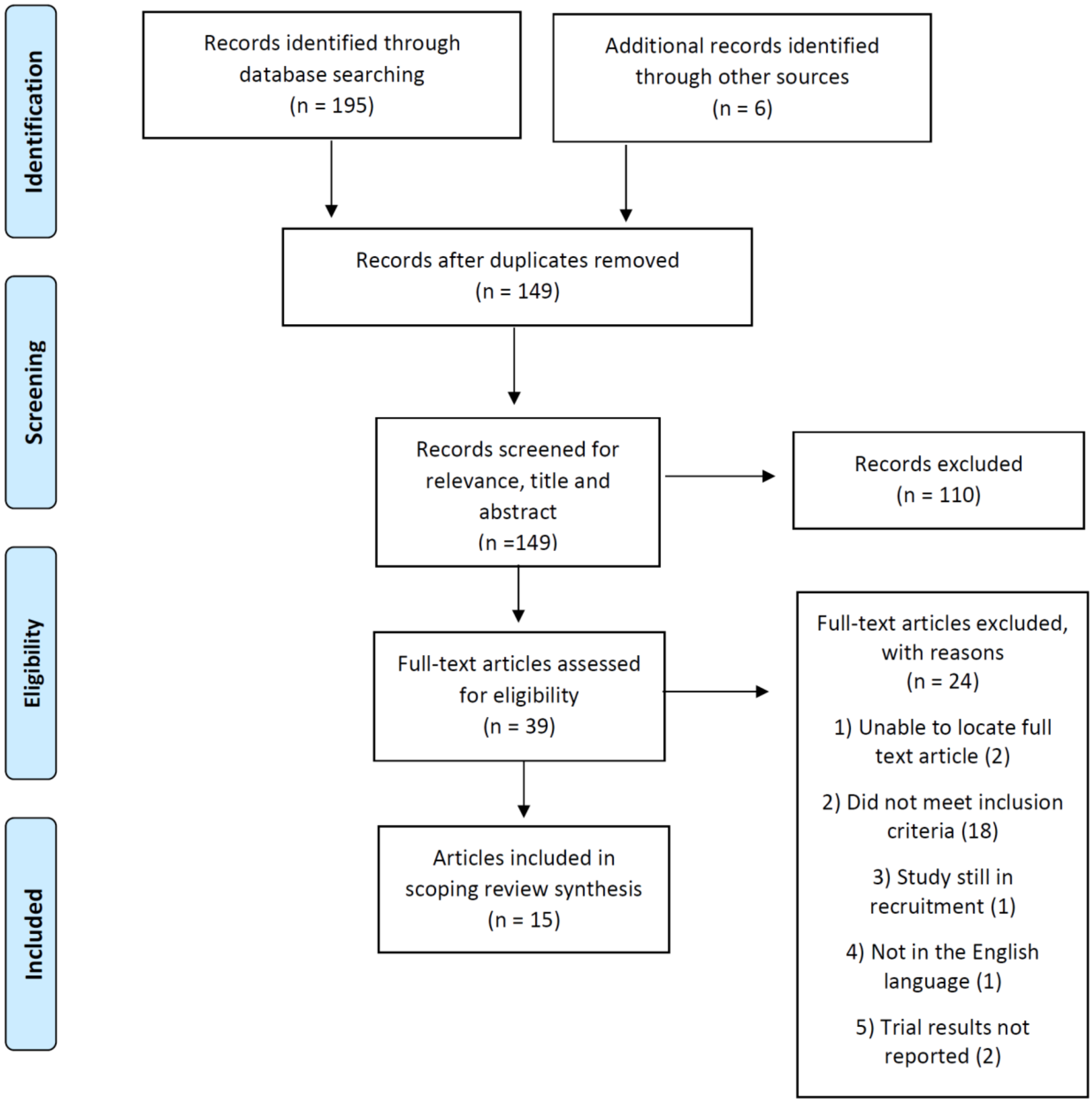

Figure 1. PRISMA flowchart of NAVA scoping review

Table 1. Included articles of scoping review (n=15)

Author, year	Country	Aim / Hypothesis	Population and Sample	Methodology
		Research Papers		
Alander, et al. 2012	Finland	Comparison of pressure, flow, and NAVA triggering in neonatal and pediatric ventilatory care.	18 children - 30 weeks gestation to 16 years. 3 relevant patient's infants with respiratory condition. 15 children in the final analysis.	Crossover RCT
Baudin, et al. 2014	Canada	Hypothesis: NAVA EAdi variability resembles most of the endogenous respiratory drive patterns seen in a control group.	10 mechanically ventilated patients (exposed to NAVA and conventional modes) and 11 control (spontaneously breathing). All patients less than 1 year (range: 1 - 4.7 months).	Retrospective data analysis
Bourdessoule, et al. 2012	Canada	NAVA improves patient-ventilator interaction in infants as compared with conventional ventilation.	10 infants (less than 1 year). Included 4 infants with respiratory failure. Patients all received PCV, PSV and NAVA.	Crossover study Conventional ventilation modes followed by NAVA
Clement, et al. 2011	USA	Neurally triggered breaths would reduce trigger delay, ventilator response times and work of breathing in paediatric patients with bronchiolitis.	23 children aged 0-24 months requiring MV with a clinical diagnosis of bronchiolitis. Excluded if less than 36 weeks gestational age, CLD, Cardiac disease, haemodynamically unstable.	Crossover, RCT.
De la Oliva, et al. 2012	Spain	Determine if NAVA improves asynchrony, ventilator drive, breath to breath variability and comfort when compared to PS.	12 paediatric patients with asynchrony; Newborn to 16 years; 5 of the 12 patients had ARF as their primary reason for admission and were less than 6 months of age.	Non-randomised cross-over trial
Duyndam, et al. 2012	Netherlands	Assessment of the feasibility of NAVA at the bedside and patient comfort when first initiated.	21 neonates and children included 4 infants less than 1 year. Only 2 had primary respiratory admission.	Prospective, observational, crossover study – non-randomised.
Kallio, et al. 2014	Finland	Evaluation of NAVA as an initial mode of ventilation when compared to conventional ventilation in respect of duration of MV and sedation use.	170 patients recruited. 161 fulfilled the protocol. Full-term newborn to 16 years – separate data not included for the patients. Inc: Needing ventilation for > 30 minutes. 14 patients had primary diagnosis of respiratory illness.	RCT

Kallio, et al 2015	Finland	Assessment of the feasibility of aiming at a peak Edi between 5 and 15mV during NAVA in clinical practice, to study the effect of age, sedation level and ventilatory settings on the Edi signal and to give some reference values for Edi during spontaneous breathing after extubation.	81 patients with Edi catheter passed to monitor electrical activity and to determine level of support. Included the whole PICU population. 22 patients <1 year with 2 having respiratory illness. 9 patient's were neonates with respiratory distress.	Retrospective data analysis
Liet, et al. 2011	France	A case series of three children with RSV on NAVA Support.	3 children: 1 month, 3 years and 28 days old with acute viral bronchiolitis.	Case series
Piastra, et al. 2014	Italy	Evaluation of NAVA feasibility and safety as compared to PS in infants with ARDS.	10 infants with ARDS and weaned with NAVA versus 20 infants with ARDS weaned with PSV – matched for age, gas exchange impairment and weight.	Nested, pilot cohort study
Review and Expert Opinion articles				
Garzando, et al. 2014	Spain	Neurally adjusted ventilator assist: An update	N/A	Literature review
KariKari, et al. 2019	USA	NAVA versus conventional ventilation in pediatric population: are there benefits?	N/A	Review and meta-analysis
Nardi, et al. 2017	France	Recent advances in Pediatric ventilator assistance	N/A	Review
Sinderby, et al. 2007	Canada	Neurally adjusted ventilator assist: An update and summary of experiences	N/A	Discussion; expert opinion article
Terzi, et al. 2012	France	Update on NAVA – a report of a round table conference	N/A	Expert opinion article

Table 2. Patient characteristics

Authors, year	Sample size and Age	Diagnosis
Alander, et al. 2012	N= 26 18 children; 8 < 1 year; 4 < 36 months.	3 with ARF
Baudin, et al 2014	N= 21 infants < 1 year; 10 in MV group and 11 in control group	4 in the MV group and 5 in the control group with ARF
Bourdessoule, et al. 2012	N= 10 infants < 1 year	4 with ARF
Clement, et al. 2011	N=23 infants 0-24 month; Mean age months 1.6 +/- 1.0.	18 infants' primary diagnosis bronchiolitis; 4 infants primary diagnosis of apneoa
De la Oliva, et al. 2012	N=12 children; 10 < 1 year, 2 >1 year.	Of the 10 infants, 5 had ARF.
Duyndam, et al. 2012	21 children; 14 <1 year; of these 14, 10 were preterm <36 weeks.	Of the 4 > 36 weeks < 1 year 2 had ARF.
Kallio, et al. 2015	N=170 children; NAVA mean age 50 months; Control mean age 39.4 months. Specific age ranges not quoted in this study.	NAVA 8% of patients had ARF; Control 6% of patients had ARF
Kallio, et al 2015	81 children; 20 of these were infants 1-12 months healthy lungs and 2 with respiratory distress. Infants < 1 month 9 with healthy lungs and 9 with respiratory distress.	1-12 months 2 with ARF and < 1 month 9 with ARF
Liet, et al. 2011	3 children; 2 of these were < 1year	2 had bronchiolitis
Piastra, et al. 2014	30 Infants; PSV group 8.5 months +/-0.7, NAVA group 7 months +/- 0.5	All had ARDS

ARF=Acute Respiratory Failure;MV=Mechanical ventilation; NAVA=Neurally adjusted ventilatory assist

Electronic Supplement Material

MEDLINE search strategy, Search results 16thJune 2020

Database	Search terms	Results
Medline	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** (Infant*) **OR** newborn infant **OR** (Bab*) **OR** (Neonate*) **AND** Acute respiratory failure **or** respiratory distress **AND** Patient ventilator interaction **or** mechanical ventilation **or** artificial ventilation	12
	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** (Infant*) **OR** newborn infant **OR** (Bab*) **OR** (Neonate*) **AND** Comfort **or** sedation **or** sedative **or** midazolam **or** morphine	16

Search	Search terms	Results
1	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** (Infant*).Ab **OR** newborn infant. Ab **OR** (Baby*).Ab **OR** (Neonate*).Ab	210
2	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** Acute respiratory failure **or** respiratory distress	104
4	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** Comfort **or** sedation **or** sedative **or** midazolam **or** morphine	64
5	NAVA. Ab **OR** Neurally adjusted ventilator assist. Ab **OR** Edi. Ab **or** EaDi. Ab **OR** electrical activity of the diaphragm.Ab **AND** Patient ventilator interaction **or** mechanical ventilation **or** artificial ventilation	182

	Database	Search term	Results
1	Medline	NAVA. Ab	371
2	Medline	Neurally adjusted ventilatory assist. Ab	220
3	Medline	Edi. Ab	2,202
4	Medline	EADi. Ab	104
5	Medline	Electrical activity of the diaphragm. Ab	340
6	Medline	(Infant*).Ab	301,572
7	Medline	Newborn infant.Ab	16,789
8	Medline	(Baby*).Ab	32,353
9	Medline	(Neonate*).Ab	76,264
10	Medline	Acute respiratory failure	7,835
11	Medline	Respiratory distress	34,052
12	Medline	Comfort	27,523
13	Medline	Sedation	35,134
14	Medline	Sedative	17,306
15	Medline	Midazolam	12,160
16	Medline	Morphine	43,472
17	Medline	Patient ventilator interaction	251
18	Medline	Mechanical ventilation	37,610
19	Medline	Artificial ventilation	2,676

Electronic supplementary material

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Terzi, et al. 2012	France	Update on NAVA – a report of a round table conference	N/A	Expert opinion article

ARDS= Acute Respiratory Distress Syndrome; ARF= Acute Respiratory Failure; CLD= Chronic Lung Disease; MV= Mechanical Ventilation; N/A=Not Applicable; NAVA=Neurally Assisted Ventilatory Assist; PCV= Pressure Controlled Ventilation; PS= pressure Support; PSV= Pressure Support Ventilation; RSV=Respiratory Syncytial Virus

Table 2. NAVA Ventilation strategies

Authors, year	Set-up of NAVA	Duration of ventilation	Initiation of NAVA
Alander, et al. 2012	Not discussed	10 mins on three different trigger modes	As soon as an Edi signal was present (initial)
Baudin, et al. 2014	Not discussed	5 hrs on NAVA, 30mins each on PSV and PCV. Data recorded in last 10 minutes.	Not discussed.
Bourdessoule, et al. 2012	Not discussed	5 hours	Not discussed
Clement, et al. 2011	NAVA level set to reflect the tidal volume in VSV.	10-minute wash in/ wash out period. 120s recording period on each mode	Weaning phase
De la Oliva, et al. 2012	NAVA level set to achieve the same maximum inspiratory pressure as in PSV.	Four sequential 10-minute recordings after 20 minutes of washout	Initial
Duyndam, et al. 2012	NAVA level set to create same peak pressure as in PSV or SIMV. PIP alarm set to 35cmH20	Not more than 3 hours, no specific or consistent times mentioned.	Initial
Kallio, et al. 2014	NAVA level set to achieve same PIP as in current mode. If on NAVA first the level was set to achieve Edi 5-15*m*v. PIP alarm set to 35cmH20.	Until extubation (3.3hrs – NAVA; 6.6 control)	Initial
Kallio, et al. 2015	NAVA level set to achieve same PIP as in current mode. If on NAVA first the level was set to achieve Edi 5-15*m*v. PIP alarm set to 35cmH20.	Until extubation (3.3hrs – NAVA; 6.6 control)	Initial
Liet, et al. 2011	NAVA level of 1.0 set to maintain Edi 5-20*m*v. If consistently above 20*m*v NAVA level increased	N/A	Initial mode
Piastra, et al. 2014	NAVA level set to deliver equivalent PIP to achieve TV of 6ml/kg/hr – Ventilator function.	Until extubation	Weaning mode following HFOV

Table 3. Measures of NAVA effectiveness

Authors, year	Significantly Affected physiological /respiratory parameters NAVA	Asynchrony	Respiratory variability observed
Alander, et al. 2012	Lower PIP	AI decreased in NAVA – cycling on and cycling off	Higher RR
Baudin, et al. 2014	None observed	Not discussed	Stable respiratory variability similar to control group when compared to PSV and PCV. Significant when compared with PCV.
Bourdessoule, et al. 2012	None observed	Lower AI in NAVA – Trigger delays. Less wasted efforts	Yes, higher in NAVA group with regards to pressure delivered
Clement, et al. 2011	Not assessed	NAVA Significantly reduced trigger delay, improved ventilator response time. Reduced PTP	Not assessed
De la Oliva, et al. 2012	Not an outcome measure	AI significantly lower in NAVA group – auto-trigger and non-triggered breaths. No reduction in double-triggering between PSV/NAVA	Yes, significantly higher in the NAVA group
Duyndam, et al. 2012	Assessed safety aspects Ventilation pressures delivered did not exceed safety parameters	Not assessed	Not assessed
Kallio, et al. 2015	Lower PIP and Fi02. Lower Oi	Not assessed	Not discussed
Kallio, et al. 2015	Higher peak and min EaDi in patients with ARF. Increased respiratory rate and decreased Tv's on NAVA.	Not assessed	Not discussed
Liet, et al. 2011	Fi02 and PIP decreased	Not assessed	Not discussed
Piastra, et al. 2014	Lower HR and MAP. Lower Pa02/Fi02 and PaC02. Lower PIP	Not assessed	Not assessed

Table 4. Sedation strategies during NAVA

Authors, year	Sedation and doses used during NAVA	Sedation score used	Effect on sedation score
Alander, et al. 2012	Not discussed	Not discussed	N/A
Baudin, et al. 2014	Not discussed	Not discussed	N/A
Bourdessoule, et al. 2012	Fentanyl, Morphine, Lorazepam	Not discussed	Not assessed
Clement, et al. 2011	COMFORT score maintained between 8-26. Sedated as per local guidance	COMFORT scale	Not discussed
De la Oliva, et al. 2012	Sedation not titrated. Stable on doses for 3 days. Medication type not identified	COMFORT scale	Comfort scales were lower in NAVA than in optimised PSV
Duyndam, et al. 2012	Midazolam, morphine, ketamine. Not titrated.	COMFORT behavioural scale	None observed
Kallio, et al. 2014	Morphine, midazolam and ketamine. Appeared to use less in NAVA group when post op patients excluded	SAS	None observed
Kallio, et al. 2015	Morphine, midazolam and ketamine. Appeared to use less in NAVA group when post op patients excluded	SAS	Aimed at sedation score of 4. A lighter level of sedation (higher SAS) and younger age were associated with higher Edi in the linear mixed model analysis, but neither the effect of NAVA level nor that of the preset PEEP reached statistical significance.
Liet, et al. 2011	Morphine weaned to 8mcg/kg/hr	Modified COMFORT scale	Modified COMFORT scale reported to have decreased on NAVA, no pre-NAVA scores provided
Piastra, et al. 2014	Remi-fentanyl and midazolam	COMFORT scale	Decrease in COMFORT scale on NAVA (p=0.004)

Figure 1. NAVA in infants with ARF – gaps in the evidence

NAVA Decision	Practice described in the included studies	Evidence gap
Initiation of NAVA ⇨	Initial Mode (22,30,31,32,33,34)	⇨ No evidence as to which patients may benefit (i) from NAVA (ii) from specific modes
	Weaning Mode (21,35)	
Setting NAVA level ⇨	Set to achieve same PIP as conventional mode (22,30,31,32)	⇨ No evidence of comparative benefit of one strategy
	Set to achieve a target tidal volume (21,35)	
	Set to maintain Edi between 5-20μv (30,31,34)	
Monitoring effectiveness ⇨	Physiological improvement (21,22,30,35,35)	⇨ No consistent outcomes measured across studies
	Respiratory improvement (21,30,33,34,35,36)	
	Patient-ventilator synchrony (21,22,33,36)	
	Work of breathing (21,33)	
Sedation practice ⇨	Titration of sedation (30,31,36)	⇨ No conclusive sedation strategy outcomes to guide practice
	Sedation score utilised (21,22,30,31,32,34,35)	