KALAM INSTITUTE OF HEALTH TECHNOLOGY

Health Technology Assessment in India (HTAIn)

सर्वे सन्तु निरामयाः।

HEALTH TECHNOLOGY ASSESSMENT

ON

Neutrally Adjusted Ventilatory Assist (NAVA) compared to Conventional Mechanical Ventilators (CVM)

KALAM INSTITUTE OF HEALTH TECHNOLOGY

ABBREVIATIONS	
NAVA	Neurally Adjusted Ventilatory Assist
CMV	Conventional mechanical ventilations
Edi	Electrical activity of the diaphragm
AI	Asynchrony Index
ARF	Acute respiratory failure
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
PAV	Proportional assist ventilation
PSV	Pressure support ventilation
PS	Pressure support
AATD	Alpha-1 antitrypsin deficiency
CAP	Community-acquired pneumonia
MSSA	Methicillin-susceptible S. aureus
LMIC	Low- and middle-income countries
PAV	Proportional Assist Ventilation
NG	Nasogastric
PEEP	Positive End-Expiratory Pressure
NIV	Non-invasive ventilation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AMSTAR	Assessment of Multiple Systematic Reviews
CD	Critical domain
NCD	Non critical domain

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Clinical Effectiveness of ICU Ventilators with Neurally Adjusted Ventilator Assist (NAVA): An Umbrella Review

Introduction

A ventilator is a device that draws carbon dioxide out of the body and pumps oxygen into the lungs to aid with breathing via an endotracheal tube, a ventilator provides air typically with a high oxygen content to a patient's lungs help to with the exchange of carbon dioxide and oxygen. A common invasive ventilation for patients experiencing respiratory failure is mechanical ventilation, which is broadly described as the body's inability to meet its needs for the removal of carbon dioxide from the body or the delivery of oxygen. Positive pressure is used in non-invasive positive pressure ventilation to give oxygen to the lungs without the need for endotracheal intubation. It is used to treat both acute and chronic respiratory failure, but to be successful and prevent consequences, careful monitoring and titration are needed. [Rochwerg].

The latest advancement is ventilatory support that is neurologically adjusted (NAVA). Innovative methods of synchronized and proportionate respiratory support include non-invasive (NIV)-NAVA and neurologically adjusted ventilatory assist (NAVA). They can facilitate patient comfort and synchronize with the respiration of the patients. To assess the electrical activity of the diaphragm (EAdi), a catheter must be inserted in order to implement NAVA. Unlike other assisted breathing modes, NAVA depends on the EAdi to start the ventilator breath and modify the ventilatory support based on the brain drive. The instantaneous EAdi and the clinician-set NAVA level define the ventilator assist amplitude. Breath by breath, the NAVA level determines when to provide instantaneous ventilator assistance by amplifying the EAdi signal [Terzi]. NAVA triggers, cycles and regulates gas delivery based on the diaphragmatic electromyography signal via a specially designed nasogastric tube. As the work of the ventilator and the diaphragm is controlled by the same signal, coupling between the diaphragm and the ventilator is synchronized. Patient ventilator asynchrony is a common problem in patients with acute respiratory failure (ARF) receiving mechanical ventilation (MV). Asynchrony has been documented in both volume and pressure assist/ control, as well as pressure support ventilation. Recent data have shown that all patients managed with conventional modes of MV have an asynchrony index > 5% at various points during the day [Blanch]. Clinicians have a hard time identifying the presence of asynchrony [Colombo]

despite the fact that numerous ineffective triggering has been associated with increased duration of mechanical ventilation.

NAVA compared to conventional mechanical ventilation which improves patient–ventilator interaction. The goal of this study was to compare outcomes with NAVA versus conventional lung-protective MV in patients with ARDS, ARF, pneumonia and COPD who are expected to require ventilatory support for at least 72 hours. (NAVA) is a partial ventilatory support mode that delivers inspiratory peak airway pressure (Paw) in proportion to the electrical activity of the diaphragm (EAdi) [Sinderby], which is obtained by the mean of an esophageal catheter containing an electrode array in front of the crural diaphragm. The magnitude of the instantaneous Paw is thus determined by the value of the instantaneous EAdi multiplied by a proportionality factor (NAVA level, in cm H2 O/μvolt) set by the clinician. The EAdi signal is correlated to the transdiaphragmatic pressure [Beck]. NAVA, therefore, delivers its assistance in proportion to the patient's inspiratory effort. Physiologic studies have consistently reported that NAVA improves patient-ventilator interactions as compared with conventional mechanical ventilation (CMV) during both invasive and noninvasive ventilation. CMV remains the most frequently used ventilatory mode for partial support ventilation [Esteban], and clinicians are thus familiar with the routine clinical appreciation of the effects of various levels of pressure support (PS). Information provided by measured respiratory efforts indices values over a wide range of NAVA levels, and their comparison with a wide range of PS levels would therefore have meaningful implications for clinicians wishing to use NAVA and for future research in this field.

Disease profile

Acute Respiratory Distress Syndrome:

ARDS is a potentially fatal disease that affects critically ill patients and is characterized by acute onset, poor oxygenation, and pulmonary infiltrates. It is an acute, diffuse, inflammatory form of lung injury. The condition is linked to widespread alveolar damage and capillary endothelial injury at the microscopic level. When there is no sign of cardiogenic pulmonary oedema, acute respiratory distress syndrome (ARDS) is characterized by bilateral lung infiltrates and severe progressive hypoxaemia that begins within seven days of the triggering event. Many risk factors exist for ARDS. Extra-pulmonary causes include sepsis, trauma, massive transfusions, drug overdoses, fat embolism, inhaling poisonous fumes, and pancreatitis in addition to pulmonary infections or aspirations. Pulmonary damage is the end

result of a chain of inflammatory reactions that is started by these extra-thoracic diseases and injuries.

Fig. 1. ARD'S: Acute lung injury

Chronic obstructive pulmonary disease:

The prevalent and treatable condition known as chronic obstructive pulmonary disease (COPD) is marked by increasing tissue damage and restricted airflow. It is linked to structural changes in the lungs brought on by long-term inflammation brought on by exposure to harmful particles or gases, most frequently cigarette smoke. Reduced lung rebound and narrowing of the airways are the results of chronic inflammation. Cough, dyspnea, and sputum production are common signs of the illness. From no symptoms to respiratory failure, there are many possible outcomes. Prolonged exposure to harmful compounds or particles causes COPD. Worldwide, smoking cigarettes is the leading cause of COPD. Alpha-1 antitrypsin deficiency (AATD), second smoking, and exposure to chemicals in the workplace and environment are possible additional causes.

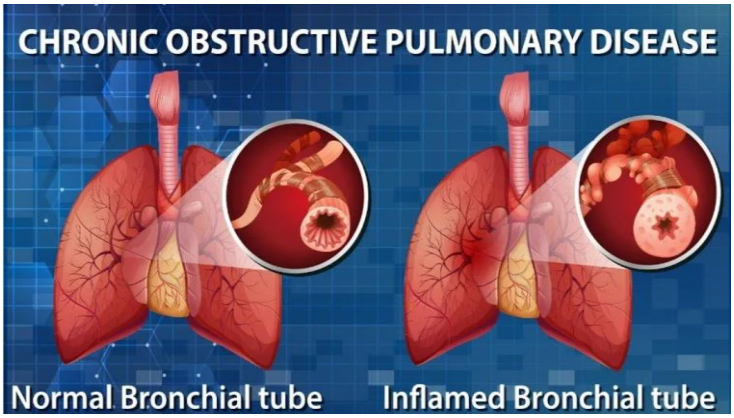


Fig. 2. Chronic obstructive pulmonary disease

Acute Respiratory Failure:

Acute respiratory failure occurs when the air sacs of the lungs cannot release enough oxygen into the blood. This can be due to fluid buildup, hardening of the air sac walls, asthma-induced muscle spasms, and many other conditions that affect lung function. Respiratory failure happens when the capillaries, or tiny blood vessels surrounding your air sacs, cannot properly exchange carbon dioxide and/or oxygen. Respiratory failure can be classified based on chronicity (i.e., acute, chronic). A thorough understanding of respiratory failure is crucial to managing this disorder. If either type of respiratory failure is not identified and addressed early, it will become life-threatening and lead to respiratory arrest, coma, and death. The approach to adult patients with suspected respiratory failure (both hypercapnia and hypoxic), as well as the diagnosis and treatment of acute and chronic respiratory failure [Vincent].

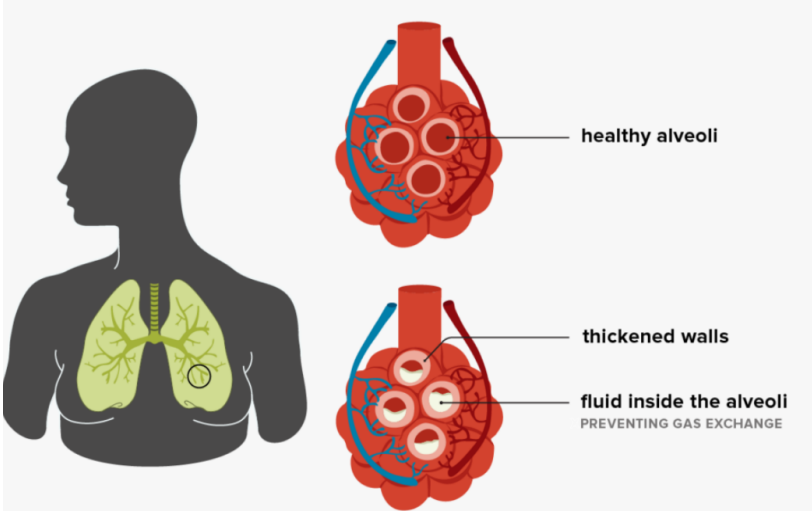


Fig. 3. Acute respiratory failure fluid builds up inside the lungs

Pneumonia:

Pneumonia is inflammation and fluid in the lungs caused by a bacterial, viral or fungal infection. It makes it difficult to breathe and can cause a fever, cough with yellow, green or bloody mucus. An acute respiratory infection that affects the distal airways and alveoli, pneumonia is a serious health issue that is linked to high rates of morbidity and both short- and long-term mortality in all age groups globally. Community-acquired pneumonia and hospital-acquired pneumonia are the two main categories of pneumonia. Pneumonia can be caused by a wide range of microorganisms, including fungus, respiratory viruses, and bacteria, and their incidence varies greatly across different geographic regions. The microbes that cause CAP and HAP are very different from one another. Streptococcus pneumoniae, respiratory viruses, Hemophilus influenzae, and other bacteria like mycoplasma pneumoniae and legionella

pneumophila are the most frequent causative pathogens in community-acquired pneumonia (CAP). Conversely, the most frequent microorganisms in hospital acquired pneumonia (HAP) are *Staphylococcus aureus* (including both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)), Enterobacterales, non-fermenting gram-negative bacilli (for example, *Pseudomonas aeruginosa*), and *Acinetobacter spp*.

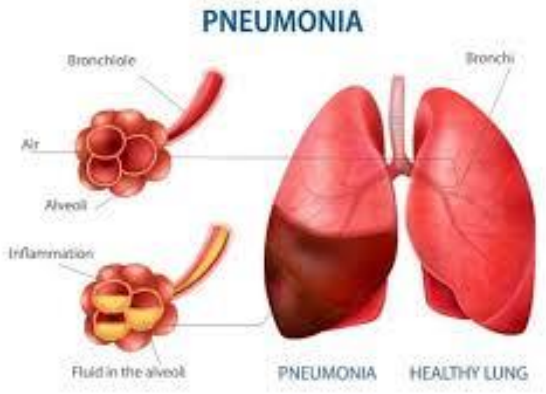


Fig. 4. Pneumonia

Epidemiology

Patients on ventilation have an incidence rate of 11.4% for ARDS, and among those with ARDS, the death rate is 41.8%. Even with a variety of treatment techniques, there is still a significant epidemiological burden. The frequency of COPD increased by 44.2% worldwide. Indian studies reported an 11.4% incidence rate of ARDS among the ventilated patients [Muhammed]. The period prevalence of mild ARDS was 30.0%, moderate 46.6% and severe, 23.4% [Giacomo]. The annual incidence of respiratory failure increased by 197%, from 429 to 1,275 cases per 100,000 persons, whereas hospital mortality decreased by 57%, from 28% to 12%. Adults, patients with pneumonia the annual incidence rates range from 1.07 to 14 per 1000 persons-years.

Economic Burden

Besides disease burden, COPD contributes to the economic burden in terms of direct and indirect costs related to disease management. The working–age group (18–65 years) patients with COPD have higher direct and indirect costs and were more resource-intensive. Economic impact in terms of direct and indirect cost is on the higher side (direct medical cost: Rs. 29,885 ± 11,995.33 or US$300–500 approximately; direct nonmedical cost: Rs. 7,441.25 ± 2,228.90 or US$90–155 approximately) and is associated with absenteeism at the job for a

significant duration of time [11]. In ARDS the economic perspectives, and mean inpatient costs ranged from $8,476 (2021 US dollars [USD]) to $547,974 (2021 USD). In Europe, pneumonia costs ~€10.1 billion annually, with inpatient care accounting for €5.7 billion, outpatient care €0.5 billion and drugs €0.2 billion and the indirect costs of lost workdays amount to €3.6 billion. The total economic burden of viral severe acute respiratory infections in patients with an early diagnosis was lower than those with a delayed diagnosis among patients with complications, both from the payer's (United States dollar [USD] 3846 million vs USD 4726 million) and societal (USD 4048 million vs USD 5020 million, respectively).

Neurally Adjusted Ventilatory Assist (NAVA):

In the relatively newer ventilation mode known as neurologically adjusted ventilatory assist (NAVA), a ventilator uses the electrical activity of the diaphragm (Edi) to produce suitable breaths and help ventilated patients. Every muscle in the body produces electrical activity to cause muscle contraction. This electrical activity is controlled by the nerve stimulation. This electrical activity is used by the NAVA ventilator to synchronize the patient's breathing efforts. Edi is the major source of the ventilator trigger and the fundamental prerequisite for NAVA to operate. Theoretically, NAVA eliminates the drawbacks of proportionate assist ventilation, including air leakage and patient and ventilator asynchrony. Variations in this electrical activity start and stop the ventilator breath. Pressure is applied in direct proportion to the Edi signal, and it stops as the signal weakens. The two variations of Edi are maximum and minimum that are displayed by the ventilator. The Edi signal is converted into the proper pressure by NAVA level. The NAVA level is given as cmHO/μV. By multiplying each Edi by the NAVA level, the ventilator will deliver pressure during ventilation. Increasing or reducing the NAVA level will vary the pressure delivery for the same Edi. On the other hand, the amount of pressure delivered varies with each breathing effort and is determined by the diaphragm's electrical activity. As a result, the patient enhances comfort and synchrony by controlling both their own and the ventilator's pressure.

Pressure Support Ventilation:

The term "conventional mechanical ventilation" describes the process of administering tidal breaths with standard target/cycling parameters through an endotracheal or tracheostomy tube using a positive pressure ventilator stated in other terms, a mechanical ventilator generates all or portion of the tidal volume. Patients who are extremely sick and have low blood oxygen levels (hypoxaemia) or high blood carbon dioxide levels (hypercapnia) need to be placed on

invasive mechanical ventilation. It is also used for the majority of patients receiving general anesthesia during surgery, as well as for patients in a coma who require airway protection to avoid aspiration (inhaling oral secretions into the lungs). Using typical trigger, target, and cycling mechanisms, the purpose is to generate or assist a tidal breath that will help sustain partial pressures of oxygen (O2) and carbon dioxide (CO2) in the arterial blood. The ventilator may be used to completely or partially perform the work of breathing [9].

Rationale of the study

A possible treatment for respiratory conditions is neurologically adjusted ventilatory assist (NAVA). In cases where respiratory mechanics are disrupted due to trauma, infection, unconsciousness, or several other circumstances, the body enters a state known as respiratory failure. When this happens, NAVA can be a life-saving treatment. While NAVA has been known to save many lives in developing countries, patients in developing countries frequently die from treatable illnesses because of a lack of funding, access to healthcare, and expertise. NAVA not only improves patient comfort and clinical outcomes but also enhances the cost-effectiveness of mechanical ventilation strategies, offering a compelling rationale for its implementation in India's healthcare system to alleviate the burden of respiratory diseases more effectively.

Technology of NAVA:

NAVA attaches a series of miniature sensors to the nasogastric tube that is normally used for patient feeding. As a result, the sensors can remain in the patient's stomach and oesophagus. The breathing signals are detected by the sensors from the diaphragm, amplified, and sent to a computer where background electrical activity is removed. The diaphragmatic activity, or Edi, is represented by this signal, which is used to adjust how much ventilation is given to the patient. The physician sets a "NAVA level" to support each diaphragmatic signal. Essentially, NAVA assist the patient in ventilator in regulating the patient's breathing. This is crucial for the patient's comfort as well as for lowering diseases related to ventilation.

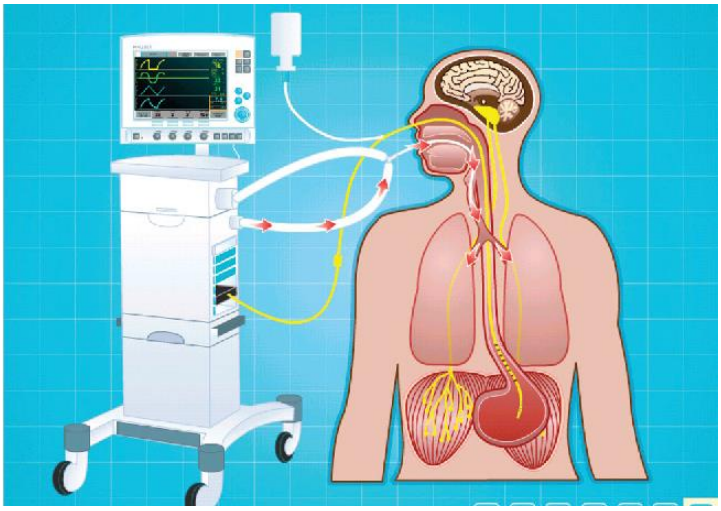


Fig: 5. Neurally Adjusted Ventilatory Assist

The Electrical Signal from the Diaphragm

The total electrical activity of the diaphragm is the EAdi signal. This EAdi signal is given in microvolts (μV) and contains the frequency and intensity of diaphragmatic muscle activity. With the use of an EAdi catheter a gastric tube with eight bipolar microelectrodes affixed to its tip—the EAdi signal is transesophageally monitored. It is situated close to the crural diaphragm, which is the measurement site for the EAdi signal. The diaphragm's electrical signals are separated from those produced by the heart, oesophagus, and other surrounding muscles using a sophisticated algorithm that produces the EAdi signal [Beck].

Before implementing mechanical ventilation with NAVA, the respiratory practitioner must properly place the EAdi catheter to obtain an accurate EAdi signal. In practice, the correct position of the electrode is determined on the basis of several criteria [Barwing].

1. The anatomical reference based on the presumed distance between the crural diaphragm and the tip, and calculated with a formula
2. The electrocardiogram signal, which can be visualized on a specific screen on the ventilator console and which, because of the aspect of the P wave and the QRS wave, is indicative of the position of the electrode
3. The synchrony of the EAdi signal with the negative deflection of the airway pressure curve in an inspiratory effort against an occluded artificial airway.

The EAdi signal should, in theory, always be detectable, with the exception of significant anatomical defects (diaphragmatic hernia, for example); central apnea without respiratory drive (diaphragmatic damage, sedation); and absence of electrical diaphragmatic activity (diaphragmatic damage, phrenic nerve damage, muscle relaxants). Dislocation of the

nasogastric tube, however, can interfere with the EAdi signal, making it difficult or impossible to continue ventilating with NAVA. Nonetheless, the ventilator has a safety feature that, in the event that no EAdi signal is received, shifts to pressure support ventilation. Furthermore, the ventilator will convert to pressure-controlled mechanical ventilation if the patient is not exhibiting spontaneous respiratory drive. This extra safety feature comes from an extra safety mechanism.

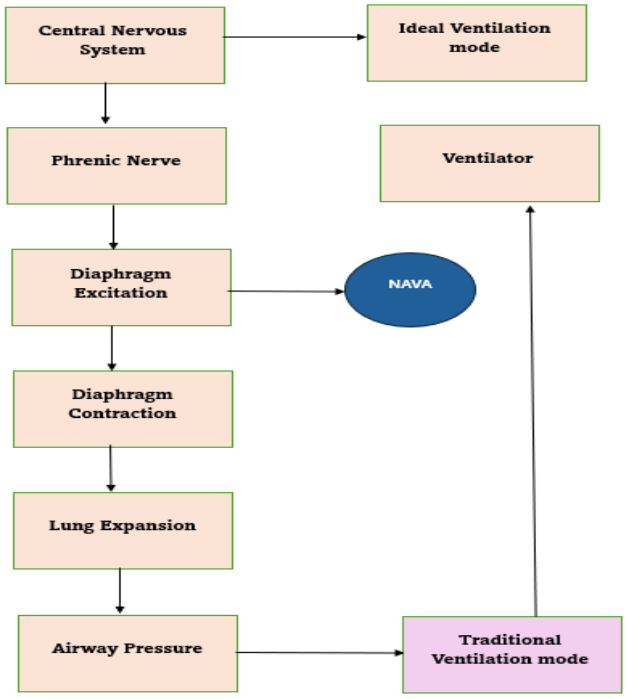


Fig: 6 Neurally adjusted ventilatory assist ventilation is triggered by the electrical activity of the diaphragm. Traditional ventilation modes are triggered by airway pressure or flow

NAVA Catheter Positioning

Reliable positioning of the NAVA catheter is important to trace a representative EAdi signal and hence offer a reliable input for ventilator assistance. The diaphragm electrical activity shown in the two central ECG leads of the catheter positioning tool during inhalation, the stability of the EAdi signal, and the lack of a p-wave on the distal lead's ECG all indicated the ideal catheter position. These recommendations stem from studies in which an accurate diaphragmatic activity was identified as an electromyographic signal from the catheter's central electrodes that was lower in root mean square and higher in central frequency [Beck]. In actuality, the signal is more effective when it originates from the electrode array's centre leads

since it avoids the electromyographic input being lost due to diaphragm displacement along the respiratory cycle.

Fig. 7. Position of the NAVA catheter in relation to the diaphragm

NAVA Ventilation

Under neutrally adjusted ventilator assist, the EAdi signal, measured in microvolts, is multiplied by a user-controlled gain factor, the NAVA level (cmH2O/V), so that at every time, the pressure delivered to the respiratory system is:

$$Paw = (NAVA\ level EAdi) + PEEP$$

The timing and intensity of the EAdi signal determine the timing and intensity of the ventilatory assist, resulting in a high level of synchrony between the neural respiratory cycle and the flow of the ventilator, both in terms of time and flow assist. The pressure delivered by the ventilator is then directly proportional to both EAdi and NAVA level, and the airway pressure–time outline accurately reflects the EAdi profile.

NAVA uses the EAdi signal as a "electric" trigger, as opposed to the majority of conventional modes of assisted mechanical ventilation, which rely only on a pneumatic trigger. The ventilator activates when the EAdi amplitude increases (typically >0.5 _V) above the baseline, and it cycles off when the signal decreases to a fixed (preset 70%) percentage of the peak value. In order to prevent over assistance, the physiological variability of respiratory drive can be preserved, patient-ventilator synchronization can be enhanced, and respiratory muscles can be unloaded by the application of an electrical trigger and cycling-off criterion.

Additionally, as EAdi is not reliant on the pressure or flow produced by the respiratory system, assisted ventilation is ensured even in the event of elevated PEEP or air leakage. [Sinderby].

EAdi as a monitoring tool

A patient's respiratory drive and neural demand for ventilatory support can be inferred from their EAdi measurement. Even in the absence of mechanical ventilation, EAdi can be constantly monitored as long as the NAVA catheter is left in place and attached to a ventilator. Regardless of NAVA's additional function as a cutting-edge ventilatory support system, the capacity to continuously monitor EAdi has improved our fundamental knowledge of respiratory physiology in both health and disease [Leiter]. In order to introduce the NAVA idea to an inexperienced ICU staff, it can be helpful to use NAVA as a monitor in conjunction with the ventilator's "NAVA preview" screen, which superimposes a predicted NAVA pressure trace on the present pressure trace. The ventilator may be used to monitor the trend in EAdi because it also has the ability to show data from the previous 24 hours. When examining how ventilatory movements affect respiratory drive, this has proven to be a very educational resource. Neural monitoring could prove to be extremely useful in a number of scenarios, such as anticipating the need for reintubation or deterioration on noninvasive ventilation (NIV), tracking respiratory recovery, assisting with spinal cord trauma prognosis, and facilitating diaphragmatic function research. Using a neuro-ventilatory efficiency index, it is possible to measure the patient's capacity to translate neural demand into tidal ventilation and determine whether this can be used as a predictor of weaning failure [Liu]. Monitoring neural demand may one day enable every patient to have a truly individualized weaning programme, tailored according to the relative impact that mobilization, airway weaning and ventilatory weaning have on their EAdi.

Improved synchrony

Asynchrony occurs when there is uncoupling of the patient’s neural demand to breathe from the ventilator’s mechanically delivered breaths. Asynchrony can occur during the inspiratory or expiratory phase. Both types of asynchrony become more pronounced with increasing levels of pressure support but not with NAVA

1. Inspiratory asynchrony occurs during the triggering phase of a breath. It occurs as a result of trigger delay or failure (for example when a patient is weak, has low respiratory drive or is over-inflated) the result of which is that a patient-demanded breath is sensed

too late or not at all. NAVA, by using neural triggering, overcomes this form of asynchrony and has the added benefit of a faster triggering time [Spahija].

2. Expiratory asynchrony occurs when ‘cycling off’ occurs inappropriately, either too early or too late. This results in either prolonged or prematurely discontinued mechanical inflation as compared to the neural respiratory cycle. This form of asynchrony has become more readily apparent as a result of EAdi monitoring and has proven to be an impediment to weaning [Terzi].

Technical Specifications of NAVA

Parameter settings

Parameter	Neonatal range	Pediatric range	Adult range
Tidal volume (ml)	2–50	10–350	100–4000
Minute volume (l/min)	0.1–7.5	0.3–20	0.5–60
Apnea, time to alarm (s)	1–45	2–45	15–45
Max. apnea time in Auto-mode (s)	3–15	3–15	7–12
Pressure level above PEEP (cmH_2O)	0–79	0–79	0–119
Pressure level above PEEP in NIV (cmH_2O)	0–60	0–60	0–60
PEEP (cmH_2O)	1–50	1–50	1–50
PEEP in NIV (cmH_2O)	2–20	2–20	2–20
CPAP pressure (cmH_2O)	2–20	2–20	–
Respiratory rate (breaths/min)	4–150	4–150	4–100
SIMV rate (breaths/min)	1–60	1–60	1–60
Breath cycle time, SIMV (s)	0.5–15	0.5–15	1–15
P_{High} (cmH_2O)	2–50	2–50	2–50
T_{High} (s)	0.2–30	0.2–30	0.2–30
T_{PEEP} (s)	0.1–10	0.1–10	0.1–10
PS above P_{High} (cmH_2O)	0–78	0–78	0–118
O_2 concentration (%)	21–100	21–100	21–100
I:E ratio	1:10–4:1	1:10–4:1	1:10–4:1
Ti (s)	0.1–5	0.1–5	0.1–5
NAVA level ($cmH_2O/\mu V$)	0–15	0–15	0–15
Edi trigger (µV)	0.1–2.0	0.1–2.0	0.1–2.0
T_{Pause} (s)	–	0–1.5	0–1.5
T_{Pause} (% of breath cycle time)	–	0–30	0–30
Flow trigger (l/min)	0–0.5	0–0.5	0–2.0
Pressure trigger (cmH_2O)	-1 to -20	-1 to -20	-1 to -20
Insp. rise time (% of breath cycle time)	0–20	0–20	0–20
Insp. rise time (s)	0–0.2	0–0.2	0–0.4
End inspiration (% of peak flow)	1–70	1–70	1–70
End inspiration (% of peak flow) in NIV	10–70	10–70	10–70
Decelerating flow pattern in VC (%)	--	0–100	0–100
Flow adaptation in VC	--	on/off	on/off

Backup parameter settings

Parameter	Neonatal range	Pediatric range	Adult range
Inspiratory tidal volume (ml)	2–50	10–350	100–4000
Pressure level above PEEP in backup (cmH_2O)	5–79	5–79	5–119
Pressure level above PEEP in NIV backup (cmH_2O)	5–60	5–60	5–60
Respiratory rate in backup (breaths/min)	4–150	4–150	4–100
I:E ratio	1:10–4:1	1:10–4:1	1:10–4:1
Ti (s)	0.1–5	0.1–5	0.1–5

Special functions

Special function	Setting range
Manual breath	Initiation of 1 breath (In SIMV mode initiation of 1 mandatory breath)
Static measurements	Insp. or exp. hold (0–30 seconds)
Nebulization	5–30 min/Continuous/Off
O_2 boost level	Off, 1–79 %
O_2 boost function	Activate O_2 boost up to 1 minute
Leakage compensation	On/Off
Circuit compensation	On/Off
Edi monitoring	In all ventilation modes, in High flow therapy and in Standby (with Edi module and Edi catheter)
Previous mode	Activates previously used mode
Backup ventilation	Backup On/Off
Apnea management	Several parameters

Disconnection / Suction

Pre-oxygenation time	Max. 2 min
Post-oxygenation time	Max. 1 min
Patient disconnected	High priority alarm activated after 1 min
Adjustable oxygen level	21 – 100 %

Monitoring and trends

Peak airway pressure	Ppeak
Pause airway pressure	Pplat
Mean airway pressure	Pmean
Driving airway pressure	Pdrive
Positive end expiratory pressure	PEEP
Continuous positive airway pressure	CPAP
Spontaneous breaths per minute	RR sp
Respiratory rate	RR
Spontaneous expiratory minute volume	MVe sp
Inspired minute volume	MVi
Expired minute volume	MVe
Leakage fraction (%)	Leakage
Inspired tidal volume	VTi
Expired tidal volume	VTe
End expiratory flow	Flowee
Measured oxygen concentration	O_2 conc
CO_2 end tidal concentration	$etCO_2$
CO_2 minute elimination	VCO_2
CO_2 tidal elimination	$VTCO_2$
Dynamic compliance	Cdyn
Static compliance	Cstatic
Inspiratory resistance	Ri
Expiratory resistance	Re
Work of breathing, ventilator	WOBvent
Work of breathing, patient	WOBpat
Elastance	E
P 0.1	P 0.1
Shallow Breathing Index	SBI
Peak Edi value	Edipeak
Average Edipeak	Edipeak average (monitoring only)
Average Edimin	Edimin average (monitoring only)
Minimum Edi value	Edimin
Ratio of expired tidal volume to predicted body weight	VT/PBW
Ratio of expired tidal volume to body weight	VT/BW
Switches to backup per minute	Backup ∑ (trended value only)
Time in backup in percent per minute	Backup % (trended value only)
Stress Index	SI

Alarms

Alarm	Neonatal range	Pediatric range	Adult range
Airway pressure (upper alarm limit)	16–90 cmH_2O	16–90 cmH_2O	16–120 cmH_2O
Airway pressure NIV (upper alarm limit)	16–70 cmH_2O	16–70 cmH_2O	16–70 cmH_2O
Respiratory rate (upper and lower alarm limits)	1–160 breaths/min	1–160 breaths/min	1–160 breaths/min
Expired minute volume (upper alarm limit)	0.02–30 l/min	0.02–30 l/min	1–60 l/min
Expired minute volume (lower alarm limit)	0.01 – 20 l/min	0.01 – 20 l/min	0.05–40 l/min
End expiratory pressure (upper alarm limit)	1–55 cmH_2O	1–55 cmH_2O	1–55 cmH_2O
End expiratory pressure (lower alarm limit)	Off, 1–47 cmH_2O	Off, 1–47 cmH_2O	Off, 1–47 cmH_2O
No patient effort (Apnea) alarm	1–45 s	2–45 s	15–45 s
	Automatic return to support mode on patient triggering		
No consistent patient effort	Yes, described in User's manual		
High continuous pressure	Yes, described in User's manual		
O_2 concentration	Set value ±5 vol% or ≤18 vol%		
Gas supply	Below 200 kPa (2.0 bar/29 PSI), above 600 kPa (6.0 bar/87 PSI)		
Battery	• Limited battery capacity: 10 min. • No battery capacity: less than 3 min • Low battery voltage.		
End tidal CO_2 (upper and lower limit)	0.5–20 %, 4–100 mmHg, 0.5–14 kPa		
Leakage too high	Yes, described in User's manual		
Technical	Yes, described in User's manual		

Autoset (alarm limits) specification

Autoset (alarm limits) specification	Invasive ventilation, controlled modes only
High airway pressure	Mean peak pressure +10 cmH_2O or at least 35 cmH_2O
Inspiratory tidal volume too high	The greater of VTi + 30 % or VTi +2 ml
Expiratory minute volume (upper alarm limit)	Mean expiratory minute volume +50 %
Expiratory minute volume (lower alarm limit)	Mean expiratory minute volume -50 %
Respiratory rate (upper alarm limit)	Mean respiratory rate +40 %
Respiratory rate (lower alarm limit)	Mean respiratory rate -40 %
End expiratory pressure (upper alarm limit)	Mean end expiratory pressure +5 cmH_2O
End expiratory pressure (lower alarm limit)	Mean end expiratory pressure -3 cmH_2O
End tidal CO_2 concentration (upper alarm limit)	Mean end tidal CO_2 concentration +25 %
End tidal CO_2 concentration (lower alarm limit)	Mean end tidal CO_2 concentration -25 %

Y sensor (option)

Y sensor (option)	Size	Weight
Y sensor module	W 154 x L 90 x H 21 mm (W 6.1" x L 3.5" x H 0.8")	280 g (0.6 lbs)
Y sensor	W 18 x L 50 x H 27 mm (W 0.7" x L 2.0" x H 1.1")	11 g
Connectors and cables	• 15 mm male and female conical connector on flow sensor according to ISO 5356-1 • Pressure port on module, pressure line, 2.0 m (6.6 ft), phthalate free PVC • Flow sensor cable, 2.0 m (6.6 ft)	
Sensor material	• Single use: PC, Polycarbonate • Reusable: PEI, Polyetherimide or PSF, Polysulfone	
Power source	Powered by the ventilator system, 4.5 W during normal operation	
Measuring method	Hot Wire Anemometer (HWA)	
Parameters	• Airway pressure • Airway flow • Inspiratory and expiratory volumes • Trigger and End inspiration	
Measuring range	• Flow: 0.12 to 32 l/min • Pressure: -40 to 120 cmH_2O	
Y sensor resistance	10 cmH_2O/l/s at 30 l/min	
Dead space	≤1 ml	
Pressure line connector	Gable mounted bulk head connector to fit tubing with an inner diameter of 3-4 mm (0.12–0.16")	

CO_2 analyzer (option)

CO_2 analyzer (option)	Size	Weight
CO_2 analyzer module	W 154 x L 90 x H 21 mm (W 6.1" x L 3.5" x H 0.8")	265 g (0.58 lbs)
Sensor (Capnostat 5)	32.0 x 47.0 x 21.6 mm (1.3" x 1.9" x 0.8")	20 g
Operating temperature	10 to 33 °C (50 to 91 °F)	
Airway adapter		10 g
Power source	Powered by the ventilator	
Connectors and cables	Sensor	2.8 m (9.2 ft) cable
Measuring method	Mainstream, dual-wavelength, non-dispersive infrared	
Parameters	• CO_2 end tidal concentration ($etCO_2$) • CO_2 minute elimination (VCO_2) • CO_2 tidal elimination ($VTCO_2$)	
Measuring range	• 0 to 100 mmHg CO_2 partial pressure • 0 to 13.3 kPa CO_2 partial pressure • 0 to 13.2 % CO_2 volume (at a barometric pressure of 1013 hPa)	
System response time CO_2	The total system response time of the CO_2 monitor when exposed first to air and then to a gas mix with 5.0 % CO_2 is <250 ms	
Warm-up time	15 s to initial CO_2 indication maximum 2 minutes to full specification	
Oxygen concentration compensation	Automatic. Values supplied from the ventilator system	
Barometric pressure compensation	Automatic. Values supplied from the ventilator system	
Digitizing rate	100 Hz	
Airway adapter dead space	• Neonatal/pediatric: <1 cm^3 • Adult: <6 cm^3	

Edi module (option)

Edi module (option)	Size	Weight
Edi module	W 154 x L 90 x H 21 mm (W 6.1" x L 3.5" x H 0.8")	0.25 kg (0.6 lbs)
Edi catheter cable	2.0 m (6.6 ft)	-
Power source	Powered by the ventilator	
Power consumption	<3 W during normal operation	
Parameters	• Edi waveform • ECG leads waveforms • NAVA estimated pressure waveform (Pedi)	

Aerogen nebulizers

Aerogen nebulizers	Pro	Solo
Size	W 50 x L 50 x H 45 mm (W 2.0" x L 2.0" x H 1.8")	W 48 x L 25 x H 67 mm (W 1.9" x L 1.0" x H 2.6")
Weight	Approx. 25 g (0.88 oz)	Approx. 14 g (0.49 oz)
Particle size	1 – 5 µm mass median aerodynamic diameter (MMAD)	
Flow rate	>0.2 (average: ~0.4) ml/min	
Max. volume	10 ml	6 ml
Residual volume	<0.1 ml for 3 ml dose	
Control cable	1.8 m (5.9 ft)	

Log function

Event log	• Alarms • Ventilator settings • Apnea periods • Maneuvers and O_2 boost
Service log	• Technical alarms • Test results • Service records • Software installation • Configuration information

Clinical Effectiveness of ICU Ventilators with Neutrally Adjusted Ventilator Assist (NAVA): An Umbrella Review

Aim

The aim of the review is to evaluate the clinical effectiveness of NAVA compared with pressure support ventilation.

Objective

To assess clinical effectiveness of the neurally adjusted ventilatory assist (NAVA) as compared with existing pressure support ventilation (PSV) in improving patient outcomes.

Keywords: Mechanical Ventilation, asynchrony, mortality and duration of ventilation

Methodology

Eligibility Criteria

Types of studies Included:

Studies included both Randomized control trails and Nonrandomized control trails which includes

- 2 Systematic reviews are included where all studies are prospective
- 1 Systematic review containing 3 RCT's are included

Inclusion Criteria: PICO

Types of participants: Adult Patients suffering with conditions like acute respiratory distress syndrome (ARDS), Chronic respiratory distress (COPD), Acute respiratory failure (ARF) and pneumonia were included in the study.

Type of intervention: Neurally Adjusted Ventilator Assist (NAVA)

Type of comparison: Pressure support ventilation (PSV)

Outcomes: Included studies assessing the following outcomes like

1. Asynchrony Index
2. Duration of Ventilation
3. Length of stay
4. Mortality

Exclusion Criteria

Articles with no information on intervention and other diseases were excluded in this review.

Literature search database

The systematic review was conducted by primary electronic database search. Searches were conducted in PubMed, Google scholar and Cochrane databases. The articles were collected in the area of health sciences without using any filters to capture different types of study designs particularly both randomized and non-randomized studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed for this project.

Screening process

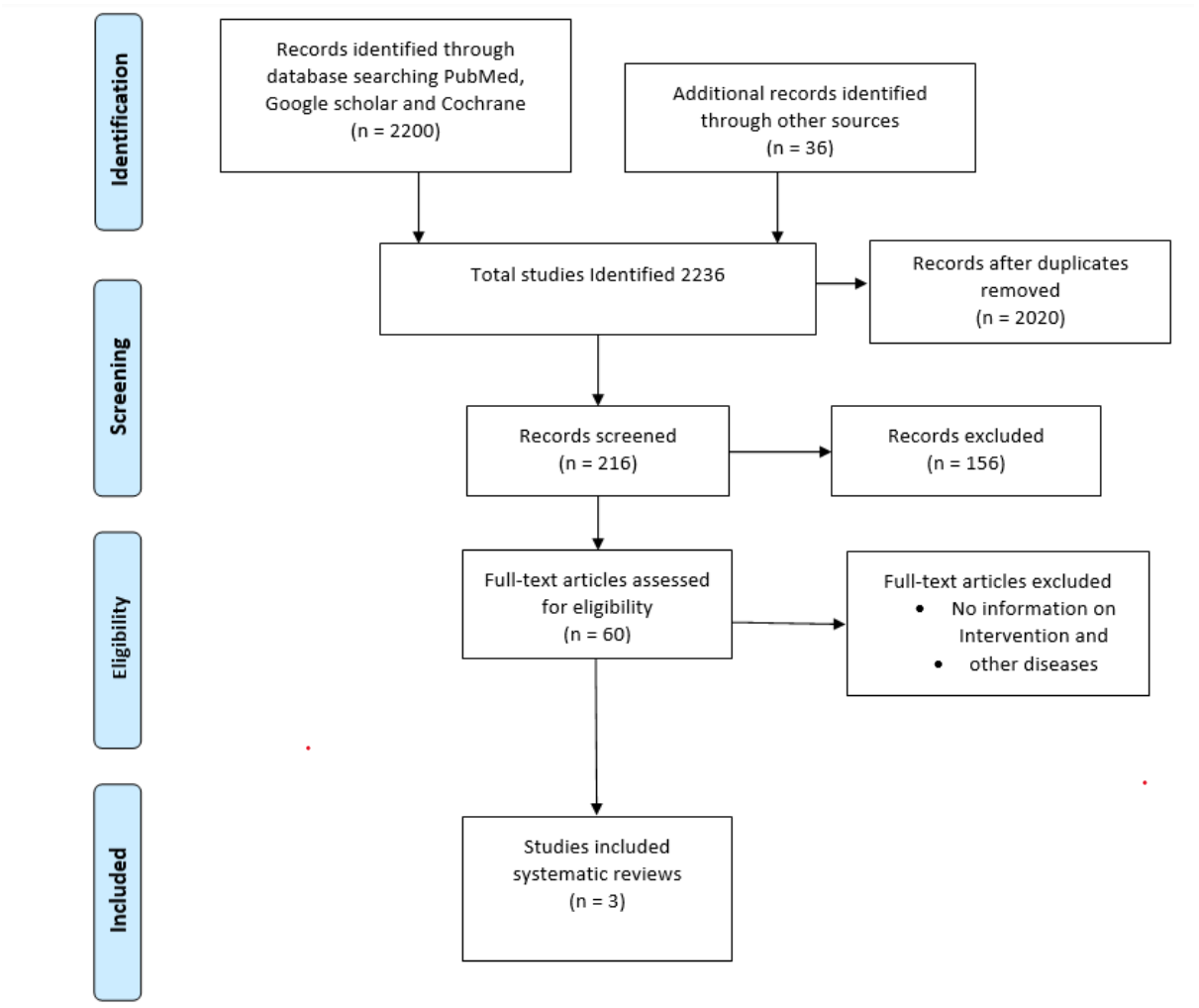
All articles identified by the search were initially screened for eligibility on title and abstracts. The search results were exported to the reference management software EndNote X7. Duplicate articles were removed, and the remaining titles and abstracts were screened. Full-text articles were retrieved and assessed for eligibility using predefined criteria, for inclusion in the review.

Data Extraction

All articles were reviewed independently, extracted into a standard Excel file, or word file then all studies that fulfilled the inclusion criteria were included and those studies that are lacking required data were excluded. Data from each eligible systematic review and meta-analysis were independently extracted by two investigators. All the results were carefully checked by a third investigator. Any discrepancy was resolved by discussion, and all discrepancies were arbitrated by a fourth reviewer. The data extraction includes

1. Description of the study device
2. Study design
3. Characteristics of participants
4. Description of the intervention
5. Description of the Comparator
6. Outcomes assessed and statistical results

PRISMA



Data Synthesis:

Based on availability of suitable statistical summary data, the combined selected outcome data in pooled meta-analyses using the Cochrane statistical software RevMan. Mean difference (MD), Risk ratios (RR) and 95% confidence intervals (CI) were calculated to estimate the impact of different outcomes like asynchrony index, duration of ventilation, length of stay and Mortality.

Results:

Study Selection:

A total of 2236 articles were identified by the search strategy of different databases like PubMed, Google scholar and Cochrane of which 2020 articles were removed based on

duplicates, 216 articles were screened. The full texts of 60 articles were screened, of which 3 systematic reviews were included in this review.

Study Characteristics:

The Articles that met the inclusion criteria were extracted from the databases among them four Articles were finally selected for different diseases like COPD, ARF, ARD and pneumonia three systematic reviews were included for conducting an umbrella review which was mentioned in below table. For categorical data mean difference and risk ratio of pooled estimates were taken for each outcome like asynchrony index, duration of ventilation, length of stay and mortality.

S.no	Author	Number of and year of publication of included studies	Data bases searched	Study objective	Population	Sample size	Type of Device (Mode)	Main results
1	Chongxiang	N=12 (2019)	PubMed, Web of Science, Scopus, and Medline	To conduct a meta-analysis comparing neurally adjusted ventilatory assist (NAVA) with pressure support ventilation (PSV) in adult ventilated patients with patient-ventilator interaction and clinical outcomes.	Adults aged above 18 years of age	331	NAVA & PSV	1. Asynchrony index (AI) 2.Duration of ventilation 3. Length of stay 4. Mortality
2	Enas	N=12 (2024)	PubMed, Embase, BioMed, and the Cochrane	To conduct a meta-analysis comparing neurally adjusted ventilatory assist (NAVA) with pressure support ventilation (PSV), in adult ventilated patients & clinical outcomes.	Adults aged above 18 years of age	799	NAVA & PSV	1. Duration of ventilation 2. Hospital mortality 3.Asynchrony index (AI)
3	Teng	N=15 (2022)	Pubmed, Cochrane Library, Web	Implement a meta-analysis to compare patient-ventilator interaction and clinical outcomes	Adults aged above 18 years of age	615	NAVA & PSV	Asynchrony Index (AI)

			of science, OpenGrey and Embase	between NAVA and pressure support ventilation (PSV) in adult patients during NIV.				

Assessment of methodological quality

AMSTAR was developed in 2007 based on the Cochrane handbook for systematic reviews of interventions. AMSTAR 2 is a domain-based rating system with seven critical domains and nine non-critical domains. AMSTAR 2 evaluates the overall quality based on performance in critical and non-critical domains, which are assigned different weights in the rating rules. The rules for appraisal of each domain by retaining only yes or no responses. However, the included studies were assessed their quality using AMSTAR 2 check list.

Two authors independently reviewed the full texts articles of each included study. The data was extracted from PubMed, Cochrane and Google scholar including publication year, journal, authors and type of study. Two authors independently used the AMSTAR 2 checklist to evaluate each included study. Disagreements were resolved by a third reviewer. The seven critical domains and nine non-critical domains are listed in the table. For all 16 domains answers were recorded. All answers were categorized as yes or no in AMSTAR 2 check list [Lin].

Detail Results for Assessment of Multiple Systematic Reviews (AMSTAR): Critical Appraisal Tool

S.no	Critical or Noncritical domain	AMSTAR 2 Checklist	Chongxiang 2019	Enas 2024	Teng 2022
1	Noncritical domain (NCD)	Did the research questions and inclusion criteria for the review include the components of PICO	Yes	Yes	Yes
2	Critical domain (CD)	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No
3	Noncritical domain	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4	Critical domain	Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes
5	Noncritical domain	Did the review authors perform study selection in duplicate?	No	No	No

6	Noncritical domain	Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7	Critical domain	Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
8	Noncritical domain	Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes
9	Critical domain	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes
10	Noncritical domain	Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11	Critical domain	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12	Noncritical domain	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the	Yes	Yes	Yes

		meta-analysis or other evidence synthesis?			
13	Critical domain	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes
14	Noncritical domain	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes
15	Critical domain	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No	Yes
16	Noncritical domain	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes
		Overall Quality of the study	Moderate	Critically low	Critically low

Sensitivity analysis

Asynchrony Index (AI)

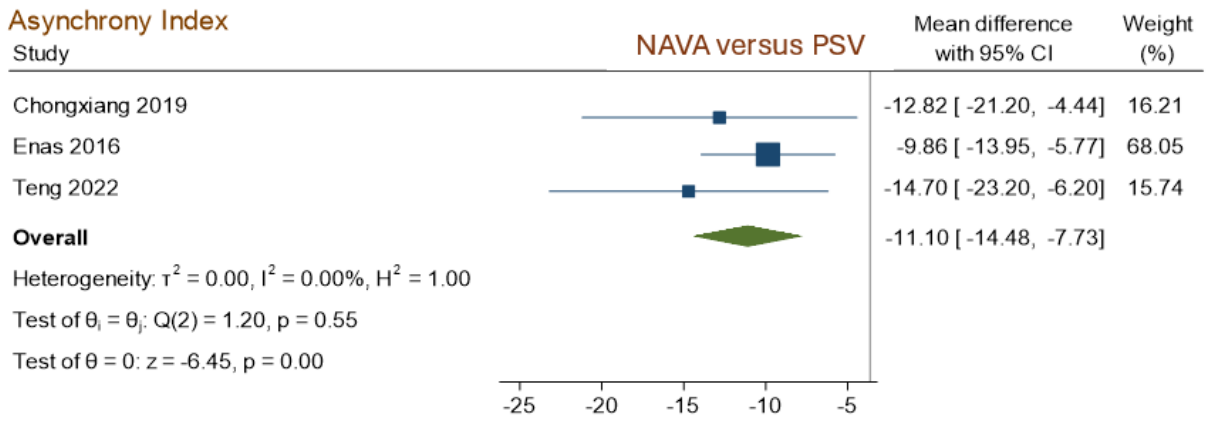


Fig. 8. Forest plot for Asynchrony Index (AI)

1. Figure shows the forest plot for point estimates and confidence interval of mean difference representing for the outcome asynchrony index with the intervention NAVA as compared with conventional mechanical ventilation.
2. The black squares represent the mean difference of individual studies, and the horizontal lines their 95% confidence intervals.
3. The area of the black squares reflects the sample size considered in the respective meta-analysis studies. The point estimates of the mean difference (represented by diamond) was computed as a weighted (using sample size) average of estimates from all the studies.
4. It was found that NAVA was associated with a significant decrease in AI relative to PSV with the MD= -11.10 (CI: -14.48, -7.73) from the meta-analysis and its CI at the bottom represented as a diamond. The meta-analysis shows that NAVA significantly reduces the outcome measure compared to PSV which is statistically significant. The centre of the diamond represents the combined treatment effect, and the horizontal tips represent the 95% CI. As the diamond is away from the line of no effect which shows that the difference found between the two groups is statistically significant.

Duration of Ventilation

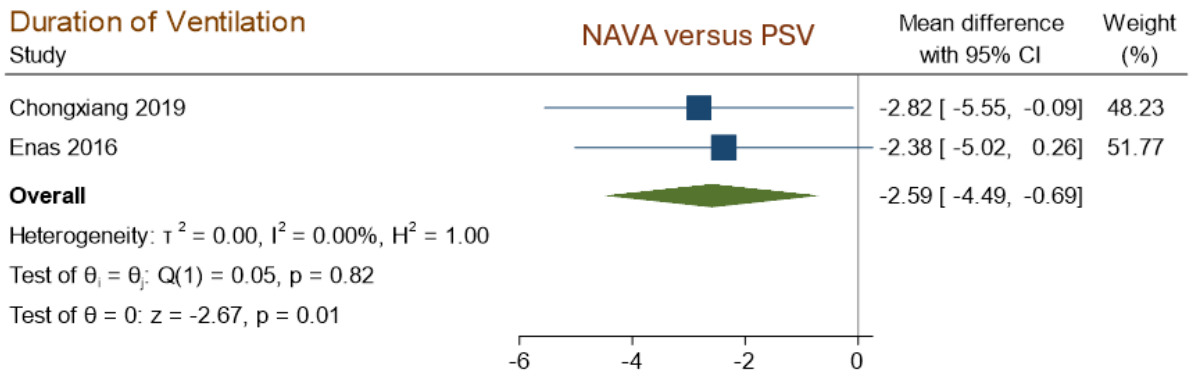


Fig. 9. Forest plot for Duration of Ventilation

1. Figure shows the forest plot for point estimates and confidence interval of mean difference representing for the outcome duration of ventilation with the intervention NAVA as compared with conventional mechanical ventilation.
2. The black squares represent the mean difference of the individual studies, and the horizontal lines their 95% confidence intervals.
3. The area of the black squares reflects the sample size considered in the respective meta-analysis studies. The point estimates of the mean difference (represented by diamond) was computed as a weighted (using sample size) average of estimates from all the studies.
4. It was found that NAVA was associated with a significant decrease in duration of ventilation on relative to PSV with the MD= -2.59 (CI: -4.49, -0.69) from the meta-analysis and its CI at the bottom represented as a diamond. The meta-analysis shows that NAVA significantly reduces the duration of ventilation measure compared to PSV. The centre of the diamond represents the combined treatment effect, and the horizontal tips represent the 95% CI. As the diamond is away from the line of no effect which shows that the difference found between the two groups is statistically significant.

Length of stay

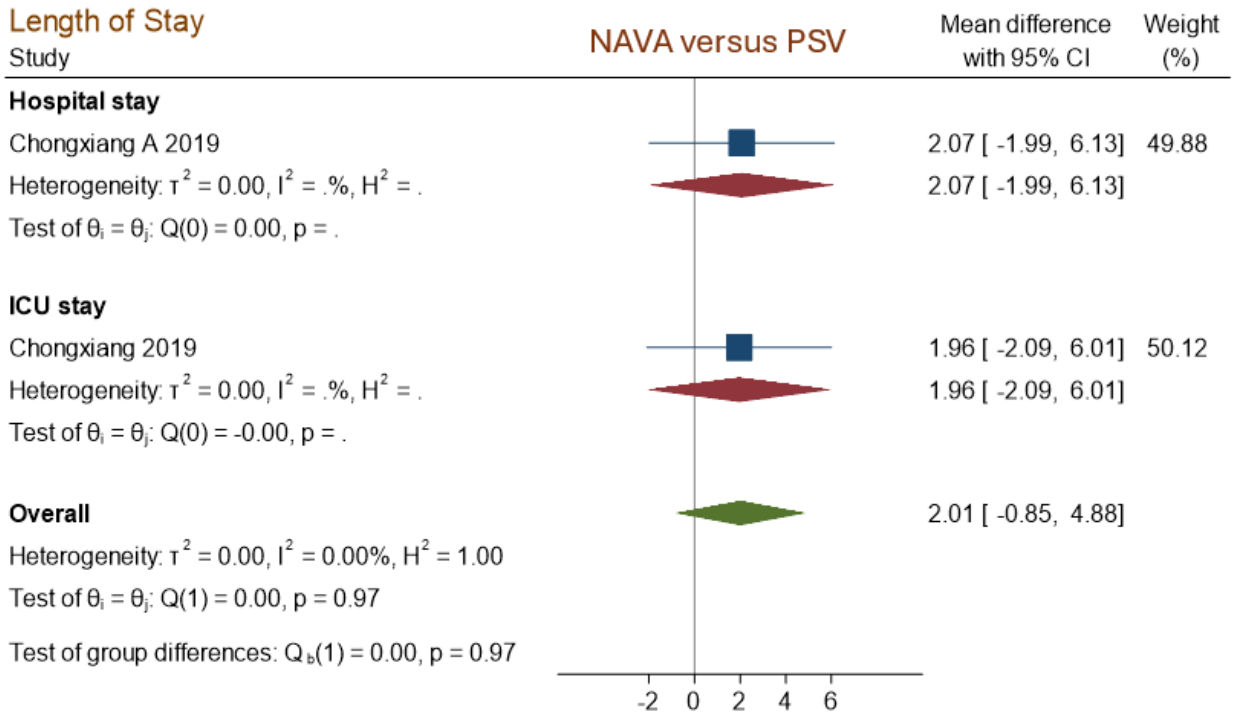


Fig. 10. Forest plot for Length of stay

1. Figure shows the forest plot for point estimates and confidence interval of mean difference representing for the outcome length of stay with the intervention NAVA as compared with conventional mechanical ventilation.
2. The black squares represent the mean difference of individual studies, and the horizontal lines their 95% confidence intervals.
3. The area of the black squares reflects the sample size considered in the respective meta-analysis studies. The point estimates of the mean difference (represented by diamond) were computed as a weighted (using sample size) average of estimates from all the studies.
4. From the above meta-analysis length of stay is not favorable with corresponds to NAVA with the (MD= 2.01 (CI: -0.85, 4.88) from the meta-analysis and its CI at the bottom represented as a diamond. The centre of the diamond represents the combined treatment effect, and the horizontal tips represent the 95% CI. As the diamond is slightly touching

the line of no effect which shows that the difference found between the two groups is not statistically significant.

Mortality

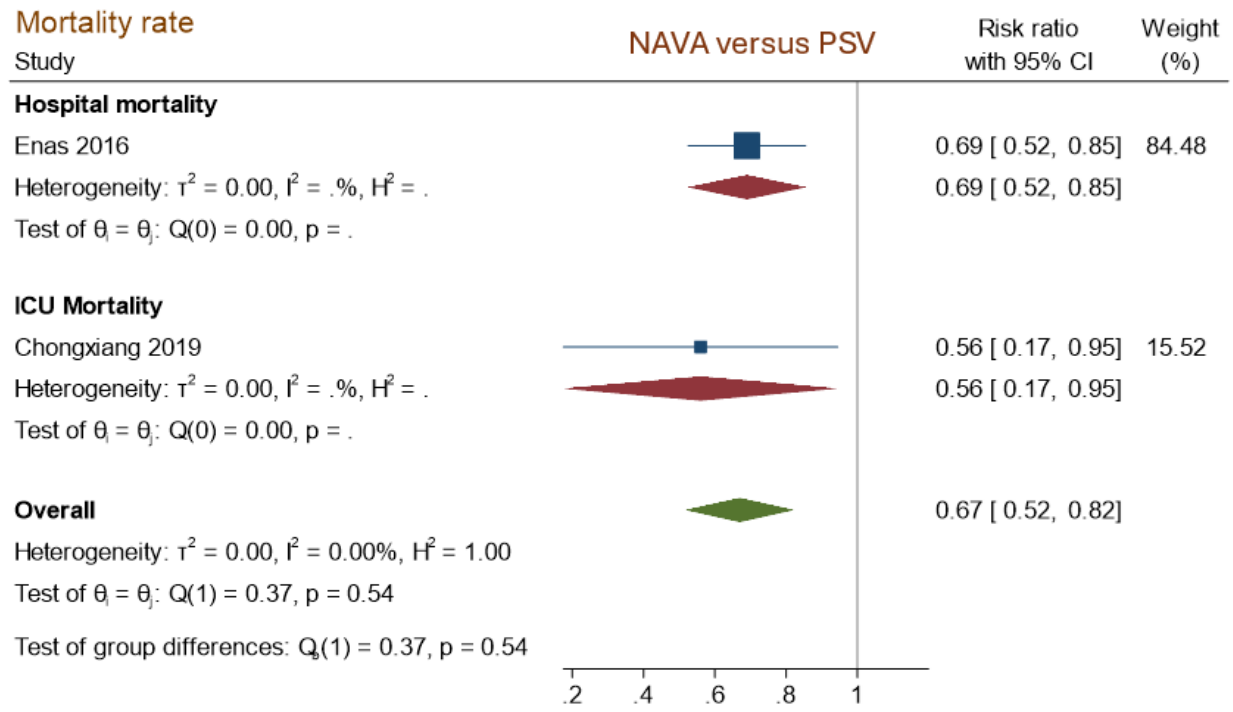


Fig: 11 Forest plot for Mortality

1. Figure shows the forest plot for point estimates (and confidence interval) of Risk ratio representing the outcome mortality with the intervention NAVA as compared with conventional mechanical ventilation.
2. The black squares represent the mean difference of the individual studies, and the horizontal lines their 95% confidence intervals.
3. The area of the black squares reflects the sample size considered in the respective meta-analysis studies. The point estimates of the risk ratio (represented by diamond) was computed as a weighted (using sample size) average of estimates from all the studies. The

effect estimate measured were risk ratio (RR) as well as the actual RR and the 95% confidence intervals (CIs).

4. The overall treatment effect RR= 0.67% (CI: 0.52, 0.82) from the meta-analysis and its CI is at the bottom and represented as a diamond. The centre of the diamond represents the combined treatment effect, and the horizontal tips represent the 95% CI. The meta-analysis therefore showed NAVA was reducing mortality by 33% as compared to PSV

Principle findings and possible explanations

This umbrella review summarized the current existing evidence from meta-analyses on both NAVA versus PSV with diverse health outcomes like asynchrony Index, duration of ventilation, length of stay and mortality rate. In this umbrella review, 3 systematic reviews are were included. NAVA puts much of the control of ventilation into the hands of the patient and allows for several advantages to be seen through this newer mode of ventilation. NAVA which controls the time and intensity of ventilation assistance through the electrical activity of the diaphragm. NAVA enhances the patient-ventilator synchrony, duration of ventilation, mortality which improves the clinical outcomes of patients in adults as compared with PSV modes.

Discussion

NAVA delivers pressure assistance proportional to and synchronized with the EAdi. A specially designed single-use feeding tube with measuring electrodes is positioned in the esophagus, enabling the isolation of diaphragmatic electrical signals from other signals in the body, especially those originating from the heart. The NAVA level is the factor by which the Edi signal is multiplied to adjust the amount of ventilator assist delivered. Utilizing the Edi waveform, NAVA can monitor neural respiratory drive and breathing patterns, providing valuable insights even without the routine techniques such as measuring airflow, airway pressure, or volume commonly employed in (PSV). NAVA can provide ventilator assistance that is synchronized in relation to triggering, also cycling the magnitude of the patient's breath. In addition, observing the EAdi and pressure waveforms can provide a real-time assessment of the degree of synchronization.

Neurally Adjusted Ventilatory Assist (NAVA) may reduce duration of mechanical ventilation and prolongs ventilator-free days- when compared with other modes- and that agree with the line of studies have reviewed changes that occur in ventilator parameters after a patient is

switched to NAVA. In this review NAVA on patient-ventilator interaction and clinical outcomes in patients with ARF, ARDS and COPD compared with pressure support ventilation modes. The key findings were that, compared with traditional modes of MV, NAVA has obvious advantages in improving the patient-ventilator interaction and decreasing the duration of MV and mortality. Neurally Adjusted Ventilatory Assist (NAVA) may reduce duration of mechanical ventilation and prolongs ventilator-free days- when compared with other modes. Studies suggest that NAVA and the Edi catheter offer a promising alternative for the management of critically ill patients receiving mechanical ventilation. The Edi waveform provides valuable information about a patient's respiratory center function, which in turn could ultimately improve patient-ventilator synchrony. It should be stated, however, that evidence-based practice dictates that additional studies will be required to better define the application and importance of NAVA in clinical practice. In this metaanalysis, forest plot was plotted for pooled values of mean differences, and risk ratio with the outcomes like asynchrony index, duration of ventilation, length of stay and mortality. For the first outcome it was found that NAVA was associated with a significant decrease in AI relative to PSV with the (MD= -11.10 (-14.48, -7.73) which shows that the difference found between the two groups is statistically significant. Second outcome was found that NAVA is associated with a significant decrease in duration of ventilation on relative to PSV with the (MD= -2.59 (-4.49, -0.69) which shows that the difference found between the two groups is statistically significant. Third outcome length of stay is not favorable with corresponds to NAVA with the (MD= 2.01 (-0.85, 4.88) which shows that the difference found between the two groups is not statistically significant. Fourth outcome mortality showed NAVA reducing mortality by 33% as compared to pressure support ventilation with the risk ratio (RR= 0.67 (0.52, 0.82).

NAVA also improves the success rate of direct weaning from the ventilator. These beneficial effects could be examined in multiple different clinical situations, such as the comfort degree of patients, depth of sedation and long-term respiratory rehabilitation. Considering that PSV is related to complications, such as a ventilator-induced lung injury and a ventilator-induced diaphragmatic dysfunction, the physiologic benefits of NAVA are expected to improve the clinical outcomes.

Conclusion

Our study suggests that NAVA enhances the synchronization of patient-ventilator and improves the clinical outcomes of patients with different modes. Neurally adjusted ventilation assist provides the potential lung and diaphragm protective ventilation. This ventilatory mode allows physiological mechanisms to minimize the probability of volutrauma and atelectrauma, patient ventilator asynchrony and myotrauma, while optimizing breathing pattern variability and patient–machine interaction. Indeed, the same beneficial effects of NAVA on lung and diaphragm protection and patient ventilator interaction might apply to proportional assist ventilation as well, since both proportional modes share the same operational principles. Setting NAVA level may be challenging in everyday clinical practice: inspiratory assist, respiratory muscle effort and unloading all need to be tailored to each patient and clinical situation. NAVA, which is based on an original physiological concept, adds new knowledge on patient-ventilator interactions during spontaneous breathing, thus helping to unravel the complex mechanisms involved in breathing control during ventilation. The short-term and long-term experience with NAVA, however, remains scant.

In this review systematic review provided definite conclusions on the clinical effect of NAVA which might further decrease the ICU mortality, duration of ventilation and better synchrony index. Furthermore, it has been manifested that NAVA could improve the success rate of direct weaning from the ventilator. In summary analysis, limited by the number of studies, underscores the need for future trials to thoroughly investigate the effects of NAVA on long-term outcomes. As a suggestion for future research, it would be beneficial to conduct large-scale studies. Large sample sizes in future research endeavors would provide more power to determine the impact of NAVA on many other outcomes conclusively.

Economic Evaluation of Neurally Adjusted Ventilatory Assist compared to Conventional Mechanical Ventilation modes for Patients with Respiratory Distress

1.Introduction

Mechanical ventilation (MV) is a critical life-saving intervention used in intensive care units (ICUs) to manage patients suffering from respiratory insufficiency. It plays a pivotal role in stabilizing respiratory function and reducing the burden on respiratory muscles, providing patients with the necessary support to recover from acute illnesses.(1) The success of MV largely depends on the underlying condition of the patient and the ventilatory strategy employed. Over the decades, the evolution of ventilatory techniques has significantly impacted patient outcomes, especially with the advancement from basic volume-controlled ventilation to more sophisticated modes aimed at improving patient-ventilator synchrony.(2)

MV serves as a supportive therapy for critically ill patients. In cases of spontaneous breathing, the pressure exerted on the respiratory system is a combination of the forces generated by both the patient's respiratory muscles and the ventilator. Effective patient-ventilator interaction is crucial in spontaneously breathing patients, requiring the ventilator to adapt to fluctuations in the patient's ventilatory needs and respiratory mechanics.(3)

In the early 1980s, a new generation of ventilators capable of providing assisted mechanical ventilation emerged. Modes like pressure support ventilation (PSV) and assisted spontaneous breathing aimed to synchronize the patient’s inspiratory effort with the ventilator’s delivery of inspiratory flow, thus reducing patient discomfort and improving the effectiveness of mechanical ventilation.(1) However, despite these improvements, research revealed significant challenges in achieving optimal patient-ventilator synchrony.

Asynchrony occurs when the ventilator's support does not align with the patient's natural breathing efforts. This lack of coordination between the neural timing of the patient and the ventilator during the respiratory cycle can result in poor patient-ventilator coordination, complicating the weaning process leading to discomfort, increased sedation requirements, prolonged duration of MV and longer ICU stays.(3,4)

In response to the ongoing challenges of asynchrony, the Neurally Adjusted Ventilatory Assist (NAVA) was developed. NAVA represents a cutting-edge mode of MV that directly addresses the problem of asynchrony by using the electrical activity of the diaphragm (Edi) to trigger and modulate ventilatory support. This allows the ventilator to deliver breaths that are finely tuned to the patient's own respiratory efforts, resulting in better synchrony between patient and machine.(5,6)

NAVA is adaptable and can be utilised in all age groups, including neonates, children, and adults, in any condition where conventional ventilators are normally advised. It is especially useful for managing conditions like acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure in adults, as well as respiratory distress syndrome (RDS), pulmonary hypertension, and central hypoventilation syndrome in neonates and children.(5)

The Servo-i and u ventilators are the only one compatible with NAVA alongside Servo-n neonatal ventilator and is designed to integrate this technology. This small, silent, and effective electronic ventilator with controlled settings and regulated delivery, enabling the machine to deliver set volumes in volume control ventilation. This platform allows for the treatment of all patient categories, from adults to neonates, using a single device and supporting other conventional modes of ventilation. Studies have shown that NAVA reduces the incidence of ventilator-induced diaphragm dysfunction (VIDD), lowers sedation needs, and leads to shorter durations of MV, thus increasing ventilator-free days. NAVA's approach offers a more personalized, lung- and diaphragm-protective form of ventilation, which could potentially revolutionize critical care.(5,7)

In the context of India's healthcare system, ICU admission rates are significantly influenced by the privatized nature of healthcare, with 90% of ICU beds located in private facilities. As a result, a large proportion of ICU admissions come from populations that face significant financial constraints, particularly lower-middle-income groups. It is estimated that 40% of patients requiring ICU care fall below the poverty line, highlighting the economic challenges of accessing critical care.(8) The average cost of an ICU stay in India is around $2,818 (₹211,000), with 77% of these costs being direct medical expenses.(9) This financial burden is exacerbated for families with patients requiring mechanical ventilation, as it is associated with a 25.8% increase in daily ICU costs.(10) Extended periods of MV can lead to catastrophic out-of-pocket expenses, often pushing families into severe financial distress.

In India, the burden of respiratory conditions requiring ICU care and MV is substantial, driven by the high prevalence of chronic diseases such as COPD and asthma, significant mortality rates, and considerable demands on healthcare resources. Given the significant costs associated with ICU care and MV, there is a growing need to explore the cost-effectiveness of newer ventilatory technologies, such as NAVA, compared to conventional mechanical ventilator modes.

Ventilators equipped with NAVA mode have demonstrated significant clinical effectiveness in reducing the asynchrony index (AI). This reduction contributes to improved patient outcomes by decreasing ventilator-associated complications, enabling earlier weaning, and reducing the duration of MV. By offering a more individualized approach to respiratory support, NAVA holds the potential to enhance clinical outcomes while reducing overall healthcare costs. Building on the evidence of NAVA's clinical efficacy, this study seeks to evaluate its cost-effectiveness compared to conventional ventilation modes. To the best of our knowledge, no economic evaluations have been conducted to assess the cost-effectiveness of NAVA compared to pressure support ventilation ventilation (PSV) modes. To address this gap in the evidence, this study aims to perform a comprehensive economic evaluation of NAVA compared to PSV modes for patients with respiratory distress in India, from the healthcare system's perspective, to determine whether replacing existing ventilators with NAVA-supporting ventilators is a viable decision.

2. Methodology

A decision tree will be used to compare both ventilation modes for this purpose.

2.1 Population

The study targets patients (both adult & pediatric) who require mechanical ventilation support in intensive care units (ICUs) for respiratory distress.

2.2 Intervention

Neurally Adjusted Ventilatory Assist (NAVA)

2.3 Comparator

Conventional Mechanical Ventilation (CMV) modes like pressure support ventilation (PSV), Proportional Assist Ventilation (PAV+), Proportional Pressure Support (PPS), and Adaptive Support Ventilation (ASV)

2.4 Outcomes

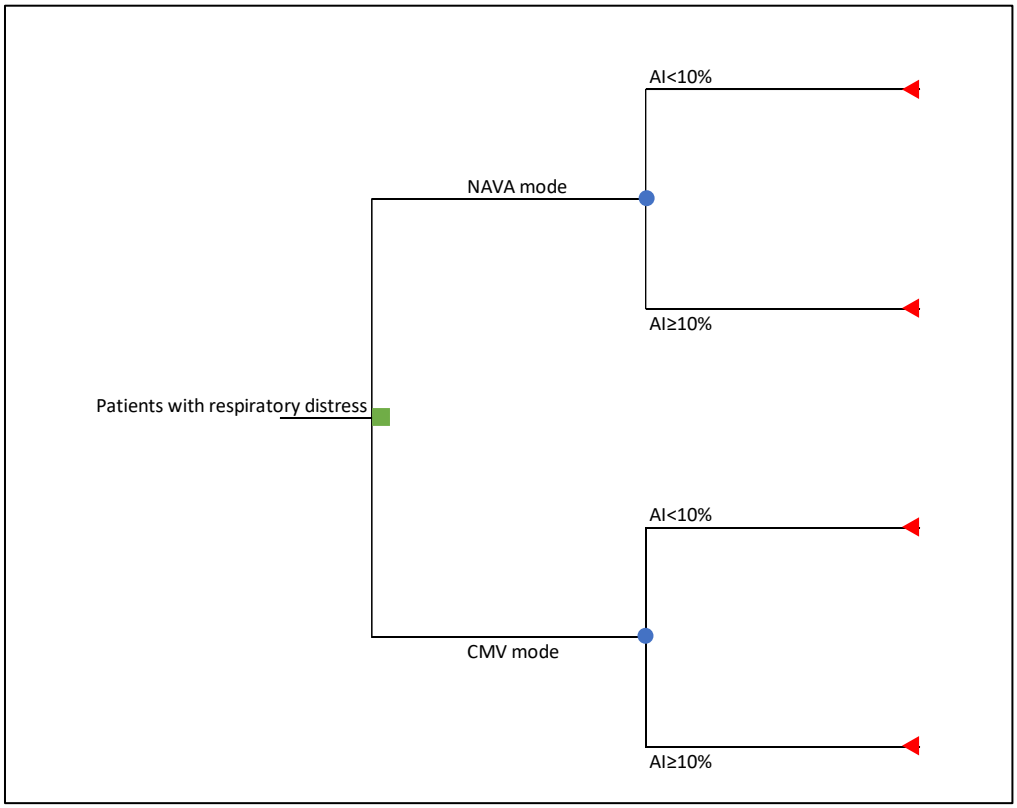
Incremental Cost Effectiveness Ratio (ICER)

Net Monetary Benefit (NMB)

Reduction in duration of MV

2.5 Cost Effectiveness Analysis

2.5.1 Decision Tree Model



2.5.2 Costing

The costs are presented in 2024 INR. The cost calculation included the ICU cost per bed day to calculate the ICU cost based on the days spent on mechanical ventilation along with the Edi catheter cost for NAVA mode to calculate the total cost per patient.

2.5.3 Model Parameters

Parameters	Basecase	Lower	Upper	Source
AI≥10%_NAVA	0.20339	0.162712	0.244068	(11)
AI≥10%_CMV	0.762712	0.610169	0.915254	(11)
duration_MV_AI<10%	4	3.2	4.8	(12,13)
duration_MV_AI≥10%	11	8.8	13.2	(12,13)
ICU cost per bed day (including cost of MV)	7436.65	5949.32	8923.98	(14)
NAVA catheter cost	18607	14885.6	22328.4	(15)

2.5.4 Sensitivity Analysis

Sensitivity analysis is pivotal for assessing the impact of alterations in model parameters on the final output. One-way sensitivity analysis (OWSA) concentrates on modifying individual parameters, thereby revealing the most influential factors and enhancing the comprehension of the model's resilience to uncertainties. In tandem with OWSA, probabilistic sensitivity analysis (PSA) encompasses varying parameters across a range, offering a comprehensive understanding of how parameter uncertainty influences the model's output and unveiling intricate relationships between parameters and outcomes.

To address heterogeneity, a Monte Carlo simulation was implemented. The PSA outcomes were then utilized to create a cost-effectiveness plane, visually illustrating the proportion of outcomes considered cost-effective in comparison to a specified threshold. Additionally, an Incremental Cost-Effectiveness Ratio (ICER) scatter plot demonstrates the interplay between incremental cost and outcomes, offering a succinct representation of PSA findings.

3.Results

3.1 Base case results

	NAVA	CMV
Cost	₹ 60,518	₹ 69,451
Avg days spent on MV per patient	5.42	9.34
NMB	₹ 10,30,693	₹ 18,09,478
Incremental Cost	₹ -8,933	
Reduction in the duration of MV	3.92	
ICER	**₹ -2,282**	
Incremental NMB	₹ 7,78,785	

Table 1: Base case results

3.2 PSA Results

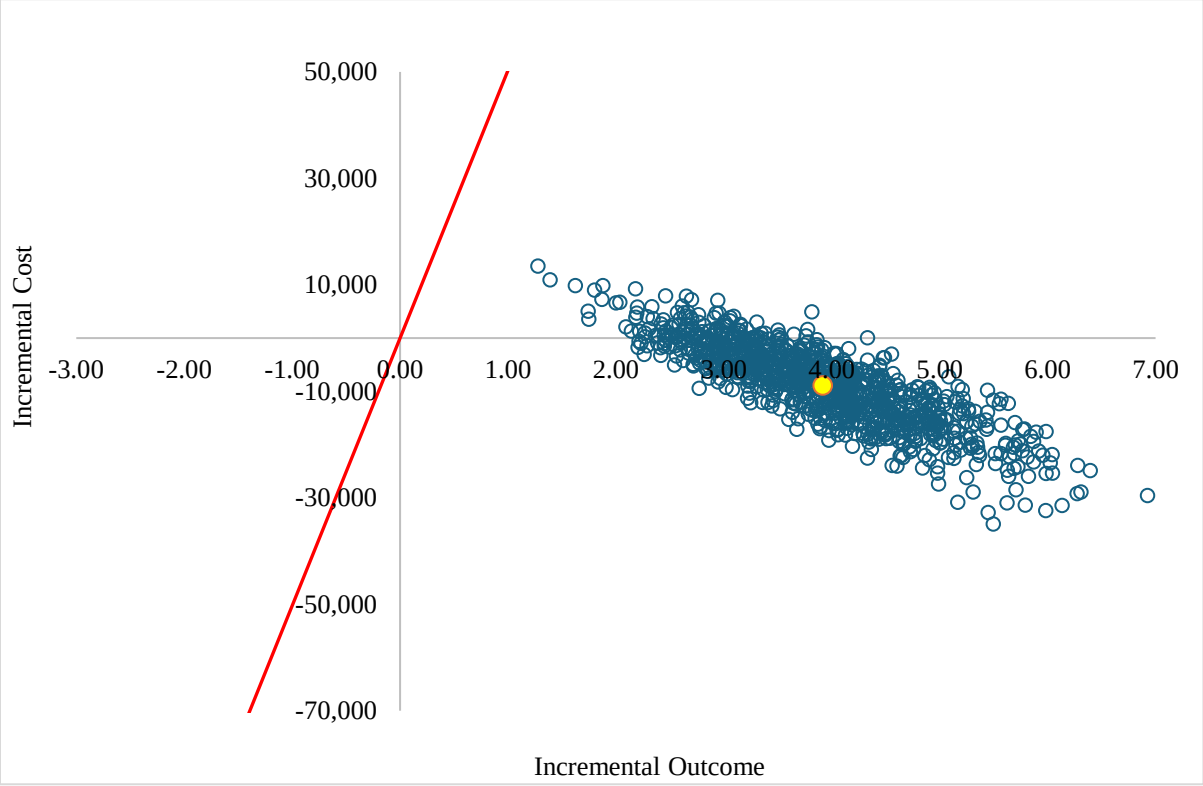


Figure 1: ICER Scatter Plot

The cost-effectiveness plane, generated through a Monte Carlo simulation with 1000 iterations, displayed the incremental cost and incremental effectiveness of NAVA compared to CMV. The ICER scatter plot showed that 89% of points fell in the southeast quadrant and 11% in the northeast quadrant, all below the Willingness-to-Pay (WTP) threshold of ₹2,01,192. This indicated that NAVA was both less costly and more effective than CMV, making it ideal for decision-makers seeking cost-saving and improved health outcomes.

The base case analysis further supported this finding, yielding an ICER of ₹ -2282, confirming NAVA as economically favorable within the threshold. To illustrate the probability of cost-effectiveness at various WTP thresholds, a Cost-Effectiveness Acceptability Curve (CEAC) was also plotted.

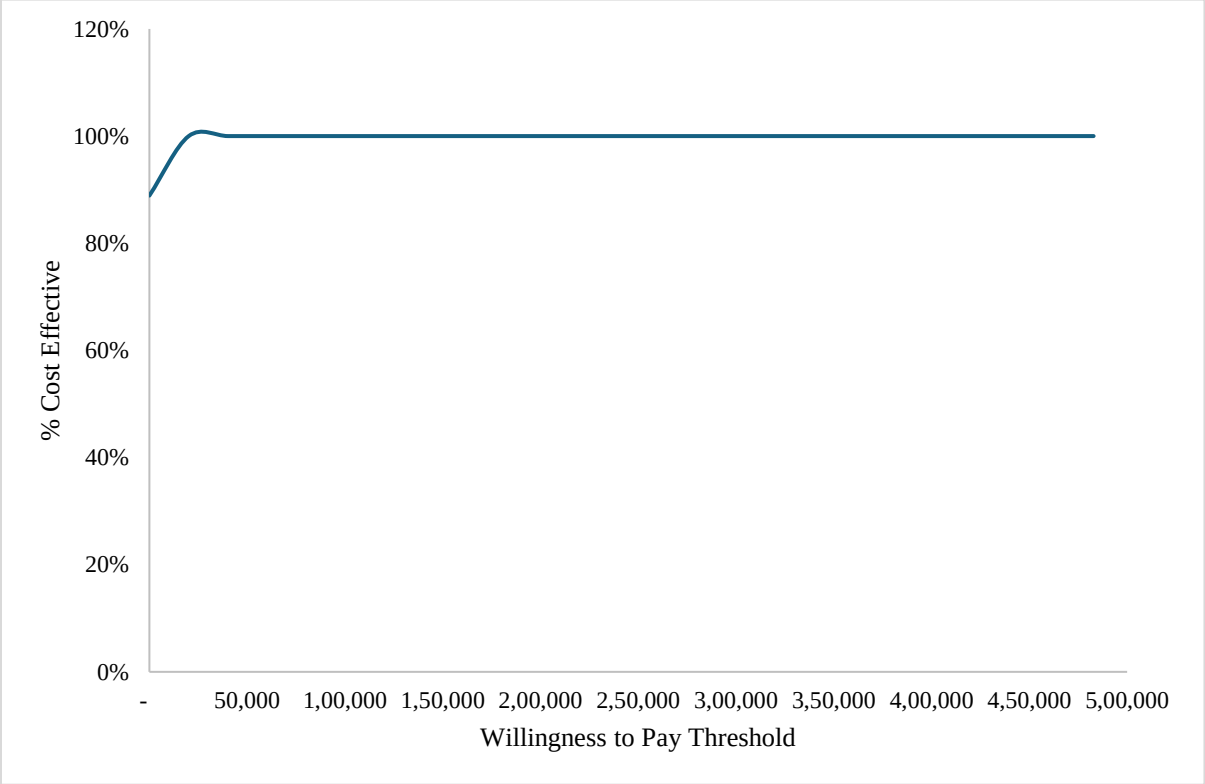


Figure 2: Cost-Effectiveness Acceptability Curve (CEAC)

The above figure illustrates the probability that NAVA is cost-effective across a range of willingness-to-pay thresholds. The curve rises quickly, approaching 100% probability at a WTP threshold as low as around 20,000, indicating a high likelihood of cost-effectiveness for NAVA at modest thresholds. This probability remains stable at nearly 100% as the WTP threshold increases,

suggesting that NAVA is a favorable economic option across all examined WTP levels in this analysis.

3.3 OWSA Results

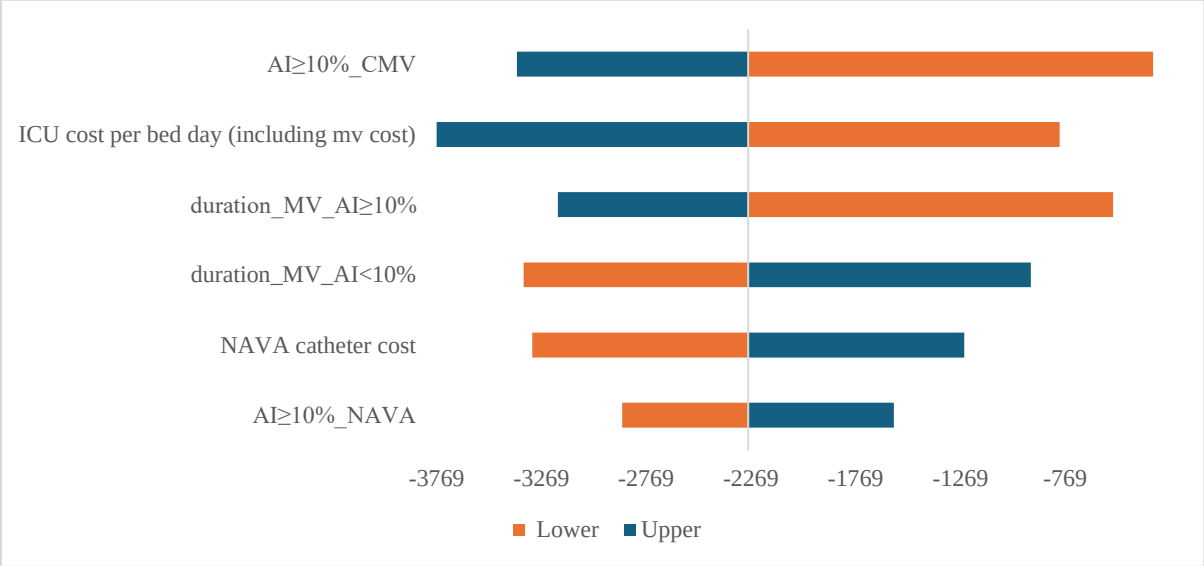


Figure 3: Tornado Plot – One way Sensitivity Analysis

The tornado plot above illustrates the impact of key parameters on the ICER. The above parameters have a considerable impact on the ICER value.

4. Discussion

This study demonstrates that NAVA is a cost-effective intervention to CMV for critically ill patients in India, assessed from a provider's perspective. The total cost per patient is also lower with NAVA compared to CMV, yielding a cost savings in terms of reduction in ventilation duration, reducing ICU stays, risk of complications associated with prolonged ventilation, and improving patient outcomes. The resulting negative ICER highlights NAVA's economic advantage, offering superior outcomes at reduced costs. The PSA further confirmed this finding, with 89% of simulations falling in the southeast quadrant, indicating that NAVA is both more effective and less costly than CMV. Our study findings concluding that, NAVA is a compelling option for healthcare systems focused on optimizing resource allocation and enhancing patient care quality.

Our findings are consistent with prior studies, including those by Chen et al. ,2019 (16) and saikiran et al.,2023 (17), which similarly reported improvements in clinical outcomes and economic efficiency with NAVA compared to traditional ventilation methods. Chen et al. found that NAVA reduced the incidence of patient-ventilator asynchrony, leading to fewer sedation requirements and shorter ICU stays, which in turn contributed to cost savings in ICU management. Saikiran et al. highlighted NAVA's ability to enhance patient comfort by aligning ventilation support with the patient's neural respiratory signals, resulting in decreased mechanical ventilation duration and improved recovery outcomes. The study conducted by Vahedi et.al,2020 (18)showing that the NAVA as a beneficial treatment option. There are researches which underscores NAVA's role in modern ventilatory support, stating its requirement for specialized equipment for global application in critical care(19).

This study's strengths include use of a decision-tree model for a thorough cost-effectiveness analysis of NAVA compared to CMV. This approach enabled a comprehensive assessment of both costs and clinical outcomes. By incorporating ventilator-free days as a primary outcome and performing sensitivity analyses, the study ensures the robustness and relevance of its findings in real-world ICU settings. These insights help decision-makers understand the potential cost savings associated with adopting NAVA, as well as the clinical benefits, such as reduced ventilator dependence and improved patient outcomes, which contribute to more efficient resource utilization in critical care. The study addresses a significant gap in the literature by focusing on the economic impact of advanced ventilation techniques in low- and middle-income countries, making the findings highly relevant for healthcare systems aiming to optimize resource allocation while improving patient outcomes.

5. Limitations

The study faced limitations due to the lack of comprehensive data on the costs of providing mechanical ventilation with and without NAVA mode. This hindered integration with existing system costs and limited the ability to analyse various scenarios individually, such as invasive versus non-invasive ventilation. Additionally, challenges in obtaining cost data and limited awareness and adoption of this mode of ventilation within the healthcare system further constrained the potential impact of the study.

6. Recommendations

Given these long-term benefits, careful consideration should be given to adopting NAVA mode ventilators, as their advantages extend beyond respiratory conditions and may prove beneficial in various clinical scenarios. Additionally, stakeholders should promote research and innovation to integrate NAVA mode into existing ventilators, which could significantly lower the costs associated with procuring new models equipped with this technology.

Future research should focus on conducting multi-centre studies to validate the cost-effectiveness of NAVA in diverse healthcare settings, considering varying ICU capacities and patient demographics. Research should also explore how different healthcare systems can optimally integrate NAVA to reduce disparities in patient care while addressing the challenges of high equipment costs and training requirements.

7. Conclusion

This study highlights the cost-effectiveness of NAVA compared to CMV for patients with respiratory distress in India. The findings suggest that the adoption of NAVA could optimize resource utilization and improve the efficiency of critical care, particularly in low- and middle-income settings like India. With appropriate training for healthcare providers, NAVA has the potential to revolutionize ventilatory management, providing better value for healthcare systems while improving patient care.

Appendix

From PubMed

Search	Query	Results
#7	Search: (((#9) AND (#3)) AND (#14)) AND (#11)	5
#6	Search: ((#9) AND (#3)) AND (#14)	77
#5	Search: (#3) AND (#14) Filters: Free full text	216
#4	Search: ((((((Mortality [MeSH Terms]) OR (death [MeSH Terms])) OR (length of stay [MeSH Terms])) OR (Hospital Stay [MeSH Terms])) OR (Stay Length [MeSH Terms])) OR (Duration ventilation [MeSH Terms]))	674,238
#3	Search: (((((Mechanical Ventilation [MeSH Terms]) OR (Artificial Respiration [MeSH Terms])) OR (Positive-Pressure Respiration [MeSH Terms])) OR (Positive-Pressure ventilation [MeSH Terms])) OR (Continuous Positive Airway Pressure [MeSH Terms])) OR (Intermittent Positive-Pressure Breathing [MeSH Terms])	91,542
# 2	Search: ((((Neurally Adjusted Ventilatory Assist [MeSH Terms]) OR (Proportional Assist Ventilation [MeSH Terms])) OR (Interactive Ventilatory Support [MeSH Terms])) OR (Assist Ventilation [MeSH Terms])) OR (Ventilation [MeSH Terms])	6,806
#1	Search: (((((((respiratory distress syndrome [MeSH Terms]) OR (Lung, Shock [MeSH Terms])) OR (acute respiratory distress syndrome [MeSH Terms])) OR (Human ARDS [MeSH Terms])) OR (respiratory distress syndrome [MeSH Terms])) OR (Bronchopulmonary dysplasia [MeSH Terms])) OR (Pneumonia [MeSH Terms])) OR (Ventilator-Associated Pneumonia [MeSH Terms])	416,715

From Cochrane

Search	Query	Results
#4	Search: ((((((Mortality [ti,ab,kw]) OR (death [ti,ab,kw])) OR (length of stay [ti,ab,kw])) OR (Hospital Stay [ti,ab,kw])) OR (Stay Length [ti,ab,kw])) OR (Duration ventilation [ti,ab,kw]))	1,234
#3	Search: (((((Mechanical Ventilation [ti,ab,kw]) OR (Artificial Respiration [ti,ab,kw])) OR (Positive-Pressure Respiration [ti,ab,kw])) OR (Positive-Pressure ventilation [ti,ab,kw])) OR (Continuous Positive Airway Pressure [ti,ab,kw])) OR (Intermittent Positive-Pressure Breathing [ti,ab,kw])	3,425
# 2	Search: ((((Neurally Adjusted Ventilatory Assist [ti,ab,kw]) OR (Proportional Assist Ventilation [ti,ab,kw])) OR (Interactive Ventilatory Support [ti,ab,kw])) OR (Assist Ventilation [ti,ab,kw])) OR (Ventilation [ti,ab,kw])	5,401
#1	Search: (((((((respiratory distress syndrome [ti,ab,kw]) OR (Lung, Shock [ti,ab,kw])) OR (acute respiratory distress syndrome [ti,ab,kw])) OR (Human ARDS [ti,ab,kw])) OR (respiratory distress syndrome [ti,ab,kw])) OR (Bronchopulmonary dysplasia [ti,ab,kw])) OR (Pneumonia [ti,ab,kw])) OR (Ventilator-Associated Pneumonia [ti,ab,kw])	26,415

From Google scholar: 945

References for Systematic Review:

1. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
2. Terzi N, Pelieu I, Guittet L et al (2010) Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. Crit Care Med 38:1830–1837.
3. Blanch L, Villagra A, Sales B et al (2015) Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 41:633–6417.

4. Colombo D, Cammarota G, Alemani M et al (2011) Observation in detect- ing patient-ventilator asynchrony. Crit Care Med 39:2452–2457.
5. Sinderby C, Navalesi P, Beck J, et al: Neural control of mechanical ventilation in respiratory failure. Nat Med 1999; 5:1433–1436 2.
6. Beck J, Gottfried SB, Navalesi P, et al: Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001; 164:419–424.
7. Vincent S. Mirabile; Eman Shebl; Abdulghani Sankari; Bracken Burns, Respiratory Failure in Adults 2023.
8. Muhammed Rashid, Manasvini Ramakrishnan, DeepaSudalai Muthu, Viji,Pulikkel Chandran , Girish Thunga, Vijayanarayana Kunhikatta, Vishal Shanbhag, Raviraja V. Acharya, Sreedharan Nair, Factors affecting the outcomes in patients with acute respiratory distress syndrome in a tertiary care setting, Clinical Epidemiology and Global Health, Vol13, 2022.
9. Giacomo Bellani, John G. Laffey, Tài Pham, Eddy Fan, Laurent Brochard, Andres Esteban, Luciano Gattinoni, Frank van Haren, Anders Larsson, Daniel F. McAuley, Marco Ranieri, Gordon Rubenfeld, B. Taylor Thompson, Hermann Wrigge, Arthur S. Slutsky, Antonio Pesenti, Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries, JAMA. 2016;315(8):788-800.
10. Beck, J.; Sinderby, C.; Lindström, L.; Grassino, A. Influence of bipolar esophageal electrode positioning on measurements of human crural diaphragm electromyogram. J. Appl. Physiol. 1996, 81, 1434–1449.
11. Barwing J, Ambold M, Linden N, Quintel M, Moerer O. Evaluation of the catheter positioning for neurally adjusted ventilatory assist. Intensive Care Med 2009;35(10):1809–1814.
12. Sinderby CA, Beck JC, Lindstrom LH, Grassino AE. Enhancement of signal quality in esophageal recordings of diaphragm EMG. J Appl Physiol 1997;82(4):1370–1377.Abstract/FREE Full TextGoogle Scholar
13. Leiter J, Manning H. The Hering-Breuer reflex, feedback control, and mechanical ventilation: the promise of neurally adjusted ventilatory assist. Crit Care Med 2010; 38:1915-16.
14. Spahija J, de Marchie M, Albert M et al. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilation assist. Crit Care Med 2010; 38:518-26.

15. Julian P T Higgins,Douglas G Altman,Peter C Gøtzsche,Peter Jüni ,David Moher, senior scientist ,Andrew D Oxman, senior researcher,Jelena Savović, postdoctoral fellow,Kenneth F Schulz, vice president, Laura Weeks, research associate, Jonathan A C Sterne, professor of medical statistics and epidemiology, Cochrane Bias Methods Group Cochrane Statistical Methods Group, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, 2011
16. Lin Li, Iriagbonse Asemota, Bolun Liu, Javier Gomez-Valencia, Lifeng Lin, Abdul Wahab Arif, Tariq Jamal Siddiqi and Muhammad Shariq Usman, AMSTAR 2 appraisal of systematic reviews and meta-analyses in the field of heart failure from high-impact journals Li et al. Systematic Reviews (2022) 11:147.
17. Chongxiang Chen, Tianmeng Wen, Wei Liao Neurally adjusted ventilatory assist versus pressure support ventilation in patient-ventilator interaction and clinical outcomes: a meta-analysis of clinical trials, Ann Transl Med 2019;7(16):382.
18. Enas W. Mahdy, Ahmed M. Abd El-Hamid, Esraa s. Abdalla, Asmaa B. E baed Neurally Adjusted Ventilatory Assist versus Pressure Support Ventilation during weaning: A meta-analysis of randomized trials, Benha medical journal, vol. XX, issue XX, 2024.
19. Teng Weiyun, Sang Linli, Cao Liuzhao, Neurally adjusted ventilatory assist (NAVA) versus pressure support ventilation (PSV) during non-invasive ventilation (NIV): systematic review and meta-analysis, Respcare 2022.

References for Economic Evaluation:

1. Neurally Adjusted Ventilatory Assist: A Ventilation Tool or a Ventilation Toy? | Respiratory Care [Internet]. [cited 2024 Oct 24]. Available from: https://rc.rcjournal.com/content/56/3/327

2. History of mechanical ventilator [Internet]. Evolution of Medical profession-Extinction of good doctors. 2019 [cited 2024 Oct 24]. Available from: https://extinctdoctorgood.com/2019/04/16/history-of-mechanical-ventilator/

3. Mirabella L, Cinnella G, Costa R, Cortegiani A, Tullo L, Rauseo M, et al. Patient-Ventilator Asynchronies: Clinical Implications and Practical Solutions. Respir Care. 2020 Nov 1;65(11):1751–66.

4. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care. 2011 Jan;56(1):25–38.

5. Shah SD, Anjum F. Neurally Adjusted Ventilatory Assist (NAVA). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Oct 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK572111/

6. NAVA [Internet]. [cited 2024 Oct 24]. Available from: https://www.getinge.com/int/products/nava/

7. The Servo ventilator story [Internet]. [cited 2024 Oct 24]. Available from: https://www.getinge.com/us/products-and-solutions/intensive-care/mechanical-ventilation/the-servo-ventilator-story/

8. Gehlot M, Mohanty S, Venkateshan M, Gomathi B, Shetty A, Das PK, et al. Socioeconomic Burden of Critically Ill Patients: A Descriptive Study. Cureus. 2023 Feb 28;15(2):e35598.

9. COST OF INTENSIVE CARE IN INDIA - PubMed [Internet]. [cited 2024 Oct 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/27608529/

10. Kaier K, Heister T, Motschall E, Hehn P, Bluhmki T, Wolkewitz M. Impact of mechanical ventilation on the daily costs of ICU care: a systematic review and meta regression. Epidemiol Infect. 2019 Jan;147:e314.

11. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Asynchrony index in pressure support ventilation (PSV) versus neurally adjusted ventilator assist (NAVA) during non-invasive ventilation (NIV) for respiratory failure: systematic review and meta-analysis. Intensive Care Med. 2016 Nov 1;42(11):1813–5.

12. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med. 2009 Oct;37(10):2740–5.

13. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med. 2015 Apr;41(4):633–41.

14. Department of Community Medicine & School of Public Health PGIMER Chandigarh [Internet]. [cited 2024 Dec 5]. Available from: https://www.healtheconomics.pgisph.in/costing_web/index.php?action=R2_database

15. Edi catheter purchase order_AIIMS.pdf [Internet]. [cited 2024 Dec 5]. Available from: https://www.aiims.edu/images/pdf/tender/itemm1.pdf

16. Chen C, Wen T, Liao W. Neurally adjusted ventilatory assist versus pressure support ventilation in patient-ventilator interaction and clinical outcomes: a meta-analysis of clinical trials. Ann Transl Med. 2019 Aug;7(16):382.

17. Neurally Adjusted Ventilatory Assist Versus Pressure Support Ventilation: A Comprehensive Review - Saikiran Mandyam, Muhammad Qureshi, Yamini Katamreddy, Devam

Parghi, Priyanka Patel, Vidhi Patel, Fnu Anshul, 2023 [Internet]. [cited 2024 Nov 12]. Available from: https://journals.sagepub.com/doi/10.1177/08850666231212807

18. Vahedi NB, Ramazan-Yousif L, Andersen TS, Jensen HI. Implementation of Neurally Adjusted Ventilatory Assist (NAVA): Patient characteristics and staff experiences. J Healthc Qual Res. 2020 Jul;35(4):253–60.

19. Verbrugghe W, Jorens PG. Neurally Adjusted Ventilatory Assist: A Ventilation Tool or a Ventilation Toy? Respir Care. 2011 Mar 1;56(3):327–35.