Neurally Adjusted Ventilatory Assist in Infants: a review article

Shih-Jou Fang, MD, Chih-Cheng Chen, MD, Da-Ling Liao, RT, Mei-Yung Chung, MD

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Title Page

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Authors: Shih-Jou Fang MD\textsuperscript{1}; Chih-Cheng Chen, MD\textsuperscript{1,2}; Da-Ling Liao, RT\textsuperscript{2}; Mei-Yung Chung, MD\textsuperscript{1,2,3}

Institutions:

\textsuperscript{1}Sections of Neonatology, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

\textsuperscript{2}Departments of Respiratory Care, Kaohsiung Chang Gung Memorial Hospital, Taiwan

\textsuperscript{3}Chang Gung University of Science and Technology, Chiayi Campus, Taiwan

Address for correspondence and reprint requests:

Mei-Yung Chung, MD

Section of Neonatology, Department of Pediatrics,

Chang Gung Memorial Hospital,
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Short running title: NAVA in infants
Abstract

Neurally adjusted ventilatory assist (NAVA) and non-invasive (NIV)-NAVA are innovative modes of synchronized and proportional respiratory support. They can synchronize with the patients’ breathing and promote patient comfort. Both techniques are increasingly being used these years, however experience with their use in newborns and premature infants in Taiwan is relatively few. As increasing evidence supports the use of NAVA and NIV-NAVA in newborns and premature infants requiring respiratory assist to achieve better synchrony, the aim of this article is to discuss whether NAVA can provide better synchronization and comfort for ventilated newborns and premature babies. In a review of recent literature, we found that NAVA and NIV-NAVA appear to be superior to conventional invasive and non-invasive ventilation. Nevertheless, some of the benefits are controversial. For example, treatment failure in premature infants is common due to insufficient triggering of electrical activity of the diaphragm (EAdi) and frequent apnea, highlighting the differences between premature infants and adults in settings and titration. Further, we suggest how to adjust the settings of NAVA and NIV-NAVA in premature infants to reduce clinical adverse events and
extubation failure. In addition to assist in the use of NAVA, EAdi can also
serve as a continuous and real-time monitor of vital signs, assisting
physicians in the administration of sedatives, evaluation of successful
extubation, and as a reference for the patient's respiratory condition
during special procedures.

Key words: neurally adjusted ventilatory assist (NAVA), NIV-NAVA,
premature infants, electrical activity of the diaphragm (EAdi), review
Main text

1. Introduction

Admitted neonates, and especially premature infants, usually require positive pressure ventilatory support during the transition period. With the administration of antenatal steroids and postnatal surfactant, most very low birth weight infants (VLBWIs) survive and need significantly long term respiratory support in the neonatal intensive care unit (NICU). Improving subject-ventilator synchrony is known to improve ventilation and decrease adverse effects. However, synchronously ventilating a premature infant is complicated because of the short inspiratory time, rapid respiratory rate, small tidal volume, and leakage around non-cuffed endotracheal tube. Neurally adjusted ventilator assist (NAVA) and non-invasive (NIV)-NAVA are innovative modes of neural-triggered ventilation that use the subject’s electrical activity of the diaphragm (EAdi) as a trigger to deliver mechanical breaths that are synchronized to each breath of the subject. NAVA and NIV-NAVA can serve a potential solution for the difficult synchrony in ventilating premature infants. However, experience with their use in newborns and premature infants is limited in Taiwan because the fee of Edi catheter was not included into national health insurance policy and
patients must pay at their own expense. In this review, we describe the reasons for using NAVA, benefits of NAVA or NIV-NAVA, and how to set and titrate NAVA mode in premature infants and neonates. Lastly, we demonstrate how to use EAdi as a real-time monitor of respiration in these patients.

2. Why NAVA? How Personalized?

Breathing is controlled by rhythmic discharge from the respiratory center of the brain which travels to excite the diaphragm muscle via the phrenic nerve, resulting in muscle contraction and movement of the diaphragm. This then leads to a reduction in airway pressure and consequently inflow of air into the lungs. Conventional synchronized mechanical ventilation involves the use of flow or pressure sensors to detect inspiration via a reversal of flow or fall in airway pressure.\(^1\) However, this reversal of flow or fall in airway pressure is the last neurorespiratory event, leading to many triggering errors with a traditional synchronized ventilator, and increased sensitivity to hyperinflation and intrinsic positive end-expiratory pressure (PEEP). Especially in neonates and premature infants, synchronized ventilation is more difficult due to the need for small tidal volume, rapid
respiratory rate and short inspiratory time. Leakage also reduces the reliability of monitoring of respiratory parameters. Moreover, neonates and premature infants have a strong vagal reflex leading to apnea and periodic breathing with a highly variable breathing pattern. In addition, traditional synchronized ventilators with present flow and pressure sensors only detect breathing initiation and deliver a preset ventilator breath. It then increases the difficulty of synchronization, especially with regards to tidal volume, breath triggering and breath termination. Mortamet et al\textsuperscript{2} described the characteristics of patient-ventilator asynchrony (PVA) in 34 critically ill children (median age 6 months) admitted to a pediatric intensive care unit (PICU) who received mechanical ventilation for at least 24 hours. In total, 9806 breaths were analyzed, and their results showed that the 27% (interquartile 22-39%) of the time was asynchronous with the ventilator, most of which was due to errors with cycling-off and delays in triggering. An automated algorithm showed an asynchrony NeuroSync index of 45%, confirming the high prevalence of asynchrony. NAVA can optimize patient-ventilator synchronization through the EAdi. With NAVA, EAdi signals are captured by the electrodes of an EAdi catheter and sent to the ventilator, which then uses the signals to help the patient breathe. Since the diaphragm
and ventilator use the same signal, mechanical coupling between the ventilator and diaphragm is almost immediate. The patient’s EAdi triggers the mechanical ventilator to deliver synchronized breaths with the initiation, size and termination of the patient’s breath. NAVA therefore offers a potential solution to many of the challenges posed by the ventilation of infants.

3. Benefits of NAVA&NIV-NAVA compared to conventional mode in infants

NAVA allows the infant rather than the ventilator or physician to regulate their own ventilation, and control the initiation, termination, size, rate and peak pressure of their breathing.³ Shi et al⁴ reviewed NAVA and NIV-NAVA articles since 2012, and found that EAdi monitoring and NAVA were safe and feasible. In comparison with conventional ventilators, NAVA provides a better gas exchange and patient-ventilator interaction, lower peak inspiratory pressure (PIP), lower oxygen requirement, and reduced respiratory muscle load. Compared with conventional non-invasive ventilation (NIV) such as nasal continuous positive airway pressure (NCPAP) and non-invasive mandatory ventilation (NIMV), non-invasive
pressure support ventilation (NIV-PS), NIV-NAVA improves synchrony, reduces reintubation, complications and oxygen requirement. Rong\textsuperscript{5} also suggested that NAVA improves comfort and requires less sedation in premature infants with bronchopulmonary dysplasia. Mally et al\textsuperscript{6} reported a reduction in patient ventilator asynchrony, as quantified using the NeuroSync index, and central apnea with NAVA compared to synchronized intermittent mandatory ventilation (SIMV) in VLBW infants. Firestone et al\textsuperscript{7} reported 17 preterm infants with apnea of prematurity, and found a decrease in clinical events from 17.9 $\pm$ 7.8/hour with CPAP to 10.2 $\pm$ 8.1/hour with NIV-NAVA of NAVA level 0 cmH2O/$\mu$V (NN0) (p=0.00047). Gibu\textsuperscript{8} also found that NIV-NAVA decreased PIP, fraction of inspired oxygen (FiO2), frequency of desaturation and EAdi compared to NIMV. The EAdi catheter was used in 11 patients for a total of 81 days without complications. Xiao and colleagues\textsuperscript{9} conducted a crossover study in which 25 infants were given CPAP and NAVA mode, and found no significant differences in hemodynamic indexes or partial pressure of carbon dioxide (PaCO2) between the two modes, and both were in normal range. Peak pressure, mean pressure, and EAdi signal were correspondingly lower in NAVA mode. Lee\textsuperscript{10} et al reported that extubation
failed within 72 hours in 6.3% of preterm infants (<30 weeks gestational age) who received NIV-NAVA and 37.5% of those who received NCPAP (p=0.041). Reviewing all of these articles (Table 1), the results show that NAVA and NIV-NAVA can improve patient-ventilator interaction and comfort, decrease PIP, oxygen requirement, sedation requirement, apnea, clinically significant events, and extubation failure. Moreover, the application of NAVA and EAdi monitoring appears to be safe and feasible in premature infants.

4. NAVA setting and titration in infants

NAVA involves the use of EAdi for patient-directed ventilatory support. Physicians set NAVA level to determine how much ventilatory support is given. In adults11,12, gradually increasing the NAVA level has been shown to increase the PIP, while keep a constant EAdi until reaching a breakpoint. A subsequent increase in the NAVA level then reduces EAdi while PIP reaches a plateau. Stein, Firestone, and LoVerde13,14,15 reported that neonates on NAVA and NIV-NAVA have the breakpoints as adults. They also found that premature infants also have intact neural feedback systems to find the breakpoint. The breakpoint is the NAVA level required to unload
the respiratory load, a condition which is the same in neonates. With regards to the regulation of NAVA level after extubation to NIV-NAVA, LoVerde et al.\textsuperscript{15} studied 15 infants for paired titration. Their results showed that the NAVA level increased, PIP plateaued at a higher level, and there was a lesser decrease in EAdi when using NIV-NAVA. The average NAVA level was 1.2 cmH2O/µV in NAVA which increased to 1.6 cmH2O/µV in NIV-NAVA, probably due to the inefficiency of NIV ventilation and leakage compensation. Hence, we suggest increasing the NAVA level 0.5-1.0 cmH2O/µV when weaning patients from NAVA to NIV-NAVA to increase PIP, and then gradually decreasing the NIV-NAVA level to 0 cmH2O/µV (NN0), which is similar to NCPAP. We choose a NIV-NAVA of NAVA level 0 cmH2O/µV (NN0) instead of NCPAP to support extubated premature infants because of the lower extubation failure rate\textsuperscript{10} and lower rate of clinically significant events\textsuperscript{7}. Apnea of prematurity (AOP) in preterm neonates is still a challenging issue. Many physicians stop using NAVA to support premature infants due to clinical deterioration from apnea. Henderson-Smart reported that 85% of preterm neonates born at 30 weeks of gestation and all of those born at <28 weeks of gestation have apnea.\textsuperscript{16} The first-line treatment for AOP is currently methylxanthines including
caffeine citrate, aminophylline and theophylline, followed by NCPAP or NIMV if the apnea remains significant. NCPAP provides constant pressure (5-8 cmH2O) throughout respiration, controlled via a demand-flow system in an expiratory valve\textsuperscript{17} or insertion of expiratory tube under water, to help the spontaneous breathing in premature neonates. However, no extra support is given to the neonate during periods of apnea, increasing susceptibility to clinically significant events such as bradycardia and desaturation. NIV-PS can provide backup ventilation in cases of apnea with no detected flow. However, NIV-PS is unreliable with regards to the trigger of flow, and occasional backup breathing occurs during spontaneous respiration. In addition, necessary backup support is not provided by the ventilator in neonates with apnea.\textsuperscript{7} Hence, a NAVA level of 0 cmH2O/\textmu V during NIV-NAVA (NN0) could be an alternative method to deliver CPAP with backup ventilation in neonates with AOP who fail CPAP.\textsuperscript{18,19} Using this method, the neonates receive little support (2cmH2O) above CPAP during spontaneous breathing, and backup ventilation during episodes of apnea. The occurrence of auto triggering has not been reported, since the mechanism of initiation is via neural triggering.\textsuperscript{7} A set apnea time ensures the ventilated infants have a minimum
spontaneous respiratory frequency. Regardless of whether NAVA or NIV-NAVA is used in premature infants, a shorter apnea time may result in more backup ventilation during periods of physiologic variability, leading to overventilation and suppressed spontaneous respiratory drive. A longer apnea time may result in a higher degree of spontaneous respiration, however it can also result in respiratory support insufficiency and more clinically significant events. Morgan\textsuperscript{20} performed a prospective, interventional study of 15 neonates <30 weeks of gestational age receiving NIV-NAVA, and analyzed the ventilator data and clinically significant events for apnea times of 2 seconds and 5 seconds for 2 hours, respectively. Compared with 5-seconds, the 2-seconds apnea time was associated with a higher rate of switching to backup ventilation from 0.5 to 2.5 switches/min (p<0.001). In addition, the time receiving backup ventilation also extended from 2%/min to 9%/min (p<0.001). However, the number of clinically significant events fell from 7 times/hour to 2 times/hour (p<0.001). A shorter apnea time led to a higher rate of switching to backup ventilation and a longer duration of backup ventilation, however it also resulted in greater clinical stability. We suggest applying a 2-seconds apnea time for premature infants <30 weeks of gestational age initially, then increasing
the apnea time as the infant grows and matures. If the apnea time can be extended to 5 seconds, the infant is ready to wean. NAVA ventilation allows the infants to control their PIP and tidal volume for each breath. There are concerns over whether a premature neonate can self-regulate tidal volume (Vt), especially when crying. Nam et al\textsuperscript{21} reported excess variability in PIP and a higher rate of excess Vt with a higher level of NAVA. However, Protain\textsuperscript{22} et al reported that the majority of breaths in premature neonates on NAVA were less than 5 ml/kg of Vt or 20 cmH\textsubscript{2}O of PIP, which are the current recommendations in neonatal guidelines. Although neonates receiving NAVA occasionally take large breaths, we suggest that these may be intermittent signs or recruiting breaths allowing for optimal lung recruitment. Protain did not find excess Vt with a higher level of NAVA, but that a lower Vt was consistent with poor lung compliance. According to these two studies,\textsuperscript{21-22} an excessively high NAVA level (>4 cmH\textsubscript{2}O/\textmu V) is still not suggested. A letter to the editor\textsuperscript{23} also pointed out that a NAVA level >2.5 cmH\textsubscript{2}O/\textmu V is possibly excessive and provides over assistance for premature infants.

5. EAdi monitoring the vital signs of a patient
Without EAdi there is no NAVA. NAVA uses the EAdi waveform to provide ventilated patients with synchronized and proportional support with invasive and non-invasive interfaces. A patients’ neural respiratory drive and breathing pattern can be monitored as a vital sign via the EAdi waveform. An increase in EAdi may indicate that the patient is not receiving adequate assistance, that there is inadequately low PEEP, worsened disease condition, agitation, or that the patient is not ready for a support ventilation mode. A decrease in EAdi may represent that the patient is receiving too much assistance, that there is a high sedation level, phrenic nerve injury, abdominal distention, or long-term conventional mode use with poor diaphragm drive. EAdi monitoring can provide clinicians with a continuous evaluation of the intensity and frequency of diaphragm activity. Iyer et al\textsuperscript{24} analyzed the EAdi values before and after extubation to predict the successful extubation rate in infants, and found that EAdi peak and $\Delta$EAdi increased after extubation in both successful and failure extubation groups. Failed extubation was associated with a smaller increase in EAdi peak and $\Delta$EAdi after extubation. Amigoni et al\textsuperscript{25} used EAdi monitoring to investigate the effects of a bolus of propofol (1 mg/kg) on the magnitude of respiratory depression in children. They found a significantly different
distribution frequency of EAdi values before and after the administration of propofol, with a mean decrease of 32%. Via EAdi monitoring, physicians can understand the degree and duration of respiration depression. With NAVA, a depression in EAdi triggers backup ventilation to prevent desaturation. The continuous monitoring of spontaneous breathing provided by the EAdi signal allows for more accurate adjustments of sedation dose, thus improves patient safety and reduced the amount of sedation used. Snow et al assessed the response to inhaled albuterol in infants with chronic lung disease by monitoring EAdi peak, EAdi min, peak pressure, mean pressure, respiratory rate, and end expiratory flow (Vee). After inhalation, the EAdi peak decreased from 38 to 10 μV, and the respiratory rate decreased from 70 to 48 breaths per minute. EAdi monitoring can therefore show whether a drug is effective or not, and provide information on adjusting the dose, frequency and when to discontinue treatment. Baudin et al used EAdi to evaluate the benefits of the prone position in infants with severe bronchiolitis requiring noninvasive ventilation. Their results showed that the prone position significantly decreased the inspiratory effort (EAdi max) and the metabolic cost of breathing (ΔEAdi). Lee et al used EAdi monitoring to investigate
the effect of skin-to-skin contact (SSC) on respiratory stabilization in premature infants. During NAVA and NIV-NAVA, EAdi peak, EAdi min, respiratory rate, time on backup ventilation, and PIP were all significantly lower in SSC than in incubator care.

EAdi monitoring can inform physicians about whether the diaphragm keeps moving under mechanical ventilation and adjust the settings accordingly to prevent excessive or insufficient support. In addition, a smaller increase in EAdi peak and ΔEAdi after extubation suggest that the patient may need more respiratory support. Moreover, precise procedural sedation with an acceptably lower EAdi signal can decrease the need for sedation. Lastly, medical treatment such as the prone position or nebulizer therapy can be evaluated via the change in EAdi. The EAdi signal can provide a personalized neural control mode, and also continuous vital sign monitoring to more precisely evaluate the patient’s status.

6. Conclusions

EAdi monitoring is an important physiological indicator which can be used to assess an infant’s breathing status in real time and continuously, allowing physicians to understand changes in respiratory work and diaphragm status, assess the extubation timing/re-intubation needs, and
sedative dosage for pain. NAVA is currently the only mode which can provide personalized ventilation according to the demands of each breath. Compared to conventional ventilation mode, it can effectively improve patient-ventilator synchrony, increase oxygenation, reduce FiO2 requirements, lower PIP and tidal volume, provide better comfort, reduce sedative use, reduce the number of days in hospital, and reduce the incidence of apnea/bradycardia/cyanosis. When using NAVA in premature infants, we recommend the following settings: NAVA level <2.5 cmH₂O/μV; upper pressure limit at 5cmH₂O above measured PIP of the patient and < 35-40 cmH₂O (=PIP 30-35 cmH₂O) as possible; apnea time 2 seconds which can be extended to 5 seconds as the patient’s condition improves. After extubation, a NIV-NAVA level of 0 can be used as a substitute for NCPAP, and studies have confirmed that it can reduce apnea and increase the success rate of extubation. The NAVA setting and titration in infants seem complicated. As a matter of fact, it is simple. We designed a flow sheet (fig.1) to make it easier for the readers to understand.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.
References


17. DiBlasi RM. Nasal continuous positive airway pressure (CPAP) for the Respir Care of the newborn infant. Respir Care 2009;54(9):1209–35.


Fig. 1 Flow sheet of NAVA setting and titration in infants
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Intervention</th>
<th>Type of study</th>
<th>n</th>
<th>Patient</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jung et al, 2016</td>
<td>NAVA/PC-SIMV+PS</td>
<td>Retrospective</td>
<td>29</td>
<td>Preterm infants&lt;1500g</td>
<td>Lower PIP, Pmean, work of breathing, and FiO2 in NAVA.</td>
</tr>
<tr>
<td>Shi et al, 2016</td>
<td>NIV-NAVA/NCPAP/NIPPV/NHFV</td>
<td>Retrospective, review</td>
<td>52</td>
<td>Preterm infants&lt;1500g</td>
<td>NAVA has better blood gas with lower PIP and FiO2.</td>
</tr>
<tr>
<td>Rong et al, 2020</td>
<td>NAVA/TRADITIONAL RESPIRATORY SUPPORT</td>
<td>Retrospective, matched cohort</td>
<td>30</td>
<td>Preterm infants&lt;1500g</td>
<td>No difference in duration respiratory support. NAVA decrease in the need of sedation.</td>
</tr>
<tr>
<td>Mally et al, 2018</td>
<td>NAVA/PC-SIMV+PS</td>
<td>Prospective, crossover</td>
<td>23</td>
<td>Infants</td>
<td>Reduction in central apnea and improved patient-ventilator interaction with NAVA.</td>
</tr>
<tr>
<td>Firestone et al, 2018</td>
<td>NIV-NAVA/</td>
<td>Retrospective</td>
<td>17</td>
<td>Preterm</td>
<td>NIV-NAVA level 0 reduced periods of</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Mode</td>
<td>Study Design</td>
<td>Sample</td>
<td>Outcome</td>
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</tr>
<tr>
<td>2020</td>
<td>NCPAP</td>
<td>Infants&lt;1500g</td>
<td>Apnea</td>
<td>Provide secure back-up rate.</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>Gibu et al,(^8)</td>
<td>NIV-NAVA/ NCPAP/HFNC/ NIMV</td>
<td>Prospective pilot</td>
<td>11 Infants&lt;2200g</td>
<td>NIV-NAVA was a safe, alternative mode that has significant reductions in PIP, FiO2, frequency of desaturations, length of desaturations, and phasic EAdi with no catheter complications.</td>
</tr>
<tr>
<td>2021</td>
<td>Xiao et al,(^9)</td>
<td>NAVA/CPAP</td>
<td>Prospective, crossover</td>
<td>25 Infants</td>
<td>PaCO2 is normal and not significantly different. Ppeak, Pmean, and mean arterial pressure are lower in NAVA.</td>
</tr>
<tr>
<td>2019</td>
<td>Lee et al,(^10)</td>
<td>NIV-NAVA/ NCPAP</td>
<td>Retrospective</td>
<td>32 Infants&lt;30wks</td>
<td>Extubation failure rate is lower in NIV-NAVA.</td>
</tr>
</tbody>
</table>
Choose size of EAdi catheter (Fr 6 for premature infants) and rinse catheter with still water

Connect EAdi cable and EAdi module, then check EAdi module function

1. Measure NEX distance and calculate the length of EAdi catheter insertion
2. Insert EAdi catheter and connect EAdi catheter to EAdi cable
3. Check EAdi catheter position on the screen of EAdi catheter positioning and make sure the EAdi catheter in good position

Begin NAVA setting

Search the Breakpoint to set NAVA level, and do not set NAVA level over 4 (Starting at NAVA level 0.5 cmH2O/µV, then NAVA level increases by 0.5 cmH2O/µV per 30 seconds of observation until the peak pressure reaches plateau and EAdi shows a downward trend, which is a Breakpoint.)

Set alarm limit at 5 cmH2O above the measured PIP of the patient, apnea time from 2 seconds, PEEP 4-6 cmH2O, FiO2 to keep PaO2 50-60 mmHg or SaO2 88-92%, trigger EAdi 0.5µV, and back up ventilation.

Try weaning when the underlying diseases improve

If the patient’s EAdi peaks usually under 10 µV, gradually lower NAVA levels with maintenance of proper tidal volumes and stable vital signs

Wean with NAVA by increasing apnea time, decreasing backup setting and decreasing NAVA level gradually

Extubate to NIV-NAVA when the apnea time was increased to 5 seconds and NAVA level was decreased to 1.0 cmH2O/µV with prompt tidal volume

Increase the NAVA level 0.5-1.0 cmH2O/µV after extubation to NIV-NAVA

Set alarm limit at 5 cmH2O above the measured PIP of the patient, apnea time from 2 seconds, PEEP 4-6 cmH2O, FiO2 to keep PaO2 50-60 mmHg or SaO2 88-92%, trigger EAdi 0.5µV, and back up ventilation

Gradually decrease the NIV-NAVA level to 0 cmH2O/µV (NN0), which is similar to NCPAP with backup ventilation