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EDITORIAL

Neurally adjusted ventilator assist in very low birth weight infants: Current status

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Abstract

Continuous improvements in perinatal care have resulted in increased survival of premature infants. Their immature lungs are prone to injury with mechanical ventilation and this may develop into chronic lung disease (CLD) or bronchopulmonary dysplasia. Strategies to minimize the risk of lung injury have been developed and include improved antenatal management (education, regionalization, steroids, and antibiotics), exogenous surfactant administration and reduction of barotrauma by using exclusive or early noninvasive ventilatory support. The most frequently used mode of assisted ventilation is pressure support ventilation that may lead to patient-ventilator asynchrony that is associated with poor outcome. Ventilator-induced diaphragmatic dysfunction or disuse atrophy of diaphragm fibers may also occur. This has led to the development of new ventilation modes including neurally adjusted ventilatory assist (NAVA). This ventilation mode is controlled by electrodes embedded within a nasogastric catheter which detect the electrical diaphragmatic activity (Edi) and transmit it to trigger the ventilator in synchrony with the patient's own respiratory efforts. This permits the patient to control peak inspiratory pressure, mean airway pressure and tidal volume. Back up pressure control (PC) is provided when there is no Edi signal and no pneumatic trigger. Compared with standard conventional ventilation, NAVA improves blood gas regulation with lower peak inspiratory pressure and oxygen requirements in preterm infants. NAVA is safe mode of ventilation. The majority of studies have shown no significant adverse events in neonates ventilated with NAVA nor a difference in the rate of intraventricular hemorrhage, pneumothorax, or necrotizing enterocolitis when compared to conventional ventilation. Future large size randomized controlled trials should be established to compare NAVA with volume targeted and pressure controlled ventilation in newborns with mature respiratory drive. Most previous studies and trials were not sufficiently large and did not include long-term patient oriented outcomes. Multicenter, randomized, outcome trials are needed to determine whether NAVA is effective in avoiding intubation, facilitating extubation, decreasing time of ventilation, reducing the incidence of

CLD, decreasing length of stay, and improving long-term outcomes such as the duration of ventilation, length of hospital stay, rate of pneumothorax, CLD and other major complications of prematurity. In order to prevent barotrauma, next generations of NAVA equipment for neonatal use should enable automatic setting of ventilator parameters in the backup PC mode based on the values generated by NAVA. They should also include an upper limit to the inspiratory time as in conventional ventilation. The manufacturers of Edi catheters should produce smaller sizes available for extreme low birth weight infants. Newly developed ventilators should also include leak compensation and high frequency ventilation. A peripheral flow sensor is also essential to the proper delivery of all modes of conventional ventilation as well as NAVA.

Key words: Interactive ventilatory support; Positive-pressure respiration; Diaphragm; Premature; Very low birth weight; Respiratory distress syndrome; Electrical diaphragmatic activity; Synchrony; Neural triggering

Core tip: Neurally adjusted ventilator assist (NAVA) ventilation utilizes the patient's neural respiratory drive to synchronize ventilatory support on a breath-by-breath basis based on the infant's ongoing needs. It appears to work well in neonates but evidence that it makes a difference in outcomes in this population has not been established so far. The majority of studies have shown no significant adverse events in neonates ventilated with NAVA nor a difference in the rate of intraventricular hemorrhage, pneumothorax, or necrotizing enterocolitis when compared to conventional ventilation. The challenge for neonatal health care providers remains the steep and prolonged learning curve for the application of NAVA.

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INTRODUCTION

Survival of more and more premature infants has occurred as a result of continuous improvements in perinatal care. Their extremely immature lungs are prone to injury with mechanical ventilation because the gas volumes/kg body weight of the lungs are small[1]. Lung injury is inversely related to gestational age[2]. This injury may develop into chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD). Strategies to minimize the risk of lung injury have been developed and include improved antenatal management (education, regionalization, steroids, and antibiotics), exogenous surfactant administration and reduction of barotrauma by using exclusive or early noninvasive ventilatory support[2,3].

The most frequently used mode of assisted ventilation is pressure support ventilation (PSV)[4-6]. Spontaneous breathing is detected by changes in airway flow or pressure in order to coordinate the ventilatory assist[7]. However, poor patient-ventilator interaction might result from conventional pneumatic triggering of the ventilator[8]. Furthermore, the potentially beneficial variability of the breathing pattern of the patient is not supported by PSV, as fixed pressure support is delivered regardless of the patients' needs[9]. This inability to provide synchrony between the patient and the assist delivered has also been demonstrated in children[10]. Patient–ventilator asynchrony has been associated with poor clinical outcome[11-15].

Changes in diaphragm structure occur following prolonged mechanical ventilation in animal models[14]. Rapid disuse atrophy of diaphragm fibers also occurs in mechanically ventilated humans[15]. This diaphragmatic muscle "disuse atrophy" "ventilator-induced diaphragmatic dysfunction" caused by sustained inactivity of the respiratory muscles (*i.e.*, passive ventilation) results in acute inflammation, loss of muscle mass, deconditioning and weakness in animal models and also in humans[6]. The preservation of spontaneous breathing during mechanical ventilation not only helps to preserve diaphragmatic function, but also to avoid atelectasis and improve oxygenation[11-15].

NEURALLY ADJUSTED VENTILATOR ASSIST

Why was neurally adjusted ventilator assist introduced and how does it work?

Over the past few years, new ventilation modes have been developed with different new strategies implemented to wean from mechanical ventilation early in order to reduce the occurrence of ventilator-induced lung injury. As patient-ventilator synchrony is essential, spontaneous patient's breathing with mechanical ventilation should be maintained whenever possible, with mechanical ventilation delivering exactly the support needed by the patient. When initiated by the patient each breath is supported immediately and that support is tailored breath-by-breath by the patient's current needs[16]. In addition, it is equally important that the level of mechanical assisted ventilation does not exceed the patient's needs. All these considerations have led to the development of neurally adjusted ventilatory assist (NAVA)[16-18]. This ventilation mode is controlled by an array of eight bipolar electrodes (sensors) electrodes embedded within a specialized nasogastric catheter positioned at the level of the crural diaphragm. These sensors detect the electrical diaphragmatic activity (Edi), and filter from electrical contamination from the heart, esophagus, and environment before

transmitting it to trigger the ventilator in synchrony with the patient's own respiratory efforts[18]. The ventilator breath is triggered and terminated by changes in this electrical activity, with the delivered inspiratory pressure proportional to the electrical signal, permitting the patient to control peak inspiratory pressure, mean airway pressure and tidal volume. In addition, as it is the patient who initiates and terminates the breaths, he also determines inspiratory (IT), expiratory times (ET) and respiratory rate, enabling flexible ventilation with breath-to-breath variability[17]. Breaths are generally initiated at 0.5 microvolt above the minimum Edi (Edi min) and terminated when the Edi signal has fallen to 70% of its peak value. The pressure curve in NAVA follows the Edi signal pattern. Back up pressure control (PC) is provided when there is no Edi signal and no pneumatic trigger. The pressure gradient (ΔP) is directly proportional to the ΔEdi following the equation (Δ P = ΔEdi × NAVA level) allowing a proportional assist mode of ventilation, which provides more support to distressed patients and permits spontaneous weaning once the lung compliance improves. NAVA levels between 1 and 4 cm H_2O/microvolt are generally used to augment respiratory support based on the size of the Edi signal aiming for normal Edi values between 5 and 10 microvolts. Therefore, if the Edi values are higher than normal, increasing ventilatory support may be considered for unloading the patient's diaphragm, while if the Edi values are lower than normal, reducing ventilatory support may be required instead in order to exercise diaphragmatic muscle fibers[18]. The tidal volume is lower than that of conventional ventilation potentially reducing lung injury and preventing disuse diaphragmatic atrophy. Failure to detect an Edi signal may result from respiratory center failure to deliver a signal (*e.g.*, apnea of prematurity, central hypoventilation syndrome, brain injury, sedation), diaphragmatic hernia, phrenic nerve conduction failure or chemical paralysis of the neuromuscular junction or the diaphragm[18]. Patients with diaphragmatic hernia are generally able to produce an Edi signal sufficient to allow assisted ventilation with NAVA[19,20].

Types of NAVA

Invasive NAVA is a complex mode of ventilation that combines NAVA, PS and PC in various proportions with short periods of apnea. Backup PC starts when the pneumatic and the neural trigger are both delayed for a period of time set by the clinician between 2 and 10 s. An automatic switch to the pressure support (PS) mode occurs in invasive NAVA modem when neural IT exceed 50% to 60% of the total respiratory time over 20 s. However, the clinician cannot set an upper limit to the IT for each breath.

Non-invasive NAVA (NIV-NAVA) is technically identical to invasive NAVA but it provides only NAVA and backup PC. Pneumatic triggers and PS are taken out of the loop because of the extremely high air leak that may reach 99% in non-invasive ventilation. Weaning occurs spontaneously but this is not the case in the backup PC mode where (PIP) is set manually. Frequent monitoring of the inspiratory pressure in NAVA should be used as a guide to select the appropriate PIP for the PC backup mode.

Advantages of NAVA

In neural triggering, the electrical trigger coming from the brain through the vagal nerve stimulates diaphragm as the same time as the ventilator, improving therefore patient-ventilator synchrony, permitting breath-to-breath variability and reducing the need for sedation[21,22]. In contrast, the pneumatic triggers used in conventional ventilation are delayed because, by definition, they occur only after the diaphragm has already contracted to generate a chest movement, a negative pressure or a positive flow. In addition neural triggering is independent of air leak around the endotracheal tube (ETT) while pneumatic triggering is sensitive to air leak. Multiple cross over trials between pressure control modes and NAVA have repeatedly shown that NAVA improves patient-ventilator synchrony in low birth weight infants, even in the presence of large air leaks[21,22]. The patient takes full control of the ventilator while receiving a timely support proportional to his own his efforts, unloading therefore the diaphragmatic muscle and reducing work of breathing[23]. This result in reduced infant fatigue and decreases the need for mandatory ventilation[16,24]. Compared with standard conventional ventilation in preterm infants, NAVA improves blood gas regulation while still using lower peak inspiratory pressure and oxygen requirements[25,26]. Edi may be used to determine optimal ventilatory support: if the infant is over-ventilated, his spontaneous respiratory drive will be suppressed resulting in a decrease of the Edi signal, while if he is under-ventilated an increased respiratory drive and higher Edi signals will result[18].

Feasibility of NAVA in very low birth weight infants

The feasibility of using NAVA in very low birth weight infants (VLBWI) was demonstrated in 2009 in a randomized crossover study on seven newborns between NAVA applied for 20 min and PSV[22]. Three other randomized crossover trials in VLBWI have compared NAVA to SIMV or PCV[23,25,27]. However they were of small sample size (n = 26, 5 and 10) and NAVA was applied for short time (4, 4 and 1 h respectively). Short-term benefits with NAVA were observed, including improved patient-ventilator synchrony and the need for a lower PIP to produce the same PaCO2. NAVA is safe mode of ventilation. The majority of studies have shown neither significant adverse events nor a difference in the rate of intraventricular hemorrhage, pneumothorax, or necrotizing enterocolitis when compared to conventional ventilation[26,28]. These were retrospective case series and randomized crossover studies with very small sample size. There are no up-to-date trials addressing

long-term outcomes.

Potential problems with NAVA

NAVA assumes that the respiratory center of preterm infants is mature enough to drive the ventilator at all times, with an appropriate rate, a sufficient magnitude and optimal IT and ET. This assumption may not hold true especially in extreme preterm infant, or during sepsis, intraventricular hemorrhage (IVH) or severe illnesses. Preterm infants demonstrate an immature response to hypercapnia[29,30], a paradoxical respiratory depression induced by hypoxemia[31] and a pronounced apneic response to laryngeal stimulation[32]. This immaturity of the respiratory drive in preterm infants very commonly results in apnea and periodic breathing in this group of neonates. These infants often produce a very small Edi signal that prevents backup ventilation with the PC mode but without producing a sufficient PIP to provide effective ventilation. This inability to generate a strong Edi may also prevent the termination of breath when the minimum Edi does not fall below 70% of the peak causing an extremely high inspiratory time. In invasive NAVA, a switch to PS takes place when the Edi signal is absent but the pneumatic trigger is still present. It occurs also when there is major discrepancy between the neural and pneumatic respiratory rates. As PS and PC are an integral part of NAVA, it is therefore incorrect to claim that NAVA is totally independent of air leak especially in VLBWI who switch frequently to PS and backup PC because of their immature respiratory drive.

A Cochrane meta-analysis demonstrated that the combination of volume targeted ventilation with PC or SIMV was associated with a statistically significant reduction of severe IVH, hypocarbia, pneumothorax, and the duration of ventilation[26]. VLBWI ventilated with NAVA keep moving back and forth between neutrally adjusted ventilation and PC backup. The non-availability of volume targeted ventilation and the fact that PIP during the backup periods is manually set by the clinician constitutes a major disadvantage of NAVA, considering the established benefits of volume targeted ventilation and the current lack of demonstrated long-term benefit of NAVA.

Capturing a strong and stable Edi signal is essential, but unfortunately, as Edi catheters for neonates are manufactured in three sizes only (6F/49 cm, 6F/50 cm and 8F/100 cm) while the length of newborns at birth is generally between 28 to 58 cm, NAVA effectiveness may not be as good as it should be. Capturing pneumatic triggers is also essential to the use of NAVA since pressure support and pressure control backup are required in case of apnea or discrepancy between pneumatic and neural triggers. Unfortunately, the flow sensor in Servo I and Servo U, which are the only ventilators providing NAVA, is located inside the machine and far from the ETT. As a result VLBWI are unable to constantly generate enough flow to compensate for the compliance of the tubing in order to trigger the ventilator. We have noticed that these patients frequently receive mandatory non-triggered breaths when they switch to the PC backup mode caused by either displacement of Edi catheter, or apnea or major discrepancy between pneumatic and neural triggers. Using a Y-peripheral flow sensor may provide a solution but must be purchased separately. The only two ventilators that offer the possibility of NAVA (servo I and Servo U) do not provide leak compensation or high frequency ventilation. This lack of versatility may become a limitation when volume targeted ventilation is required or when the clinical condition requires a change to high frequency oscillatory ventilation.

RECOMMENDATIONS

The place of NAVA in the management of respiratory distress in VLBWI is still not yet clear. We suggest that non-breathing infants should not be placed on NAVA because they do not produce a strong and consistent Edi signal to drive the ventilator. On the other hand, spontaneously breathing infants often do well on CPAP and do not require any type of ventilation. In our opinion, volume targeted ventilation in combination with PC should be the default mode of ventilation of VLBWI because it has been shown to reduce severe intraventricular hemorrhage, pneumothorax, hypocarbia and the duration of ventilation. As pressure control backup is very common in NAVA and since the long term benefits of NAVA have not yet been demonstrated in randomized trials, we recommend not to use NAVA in the first week of life in extreme low birth infants who have immature respiratory drive causing apnea and who already are at high risk of intraventricular hemorrhage and volume trauma. Larger and older infant can benefit from NAVA when they are able to generate a strong Edi activity. As NIV NAVA is presently the only ventilator mode that allows effective triggering despite the large air leak associated always present with nasal ventilation, we believe that it should be tried as a first option whenever possible. Patients with severe CLD and those who have received heavy sedation for long period may have a disuse atrophy of diaphragmatic muscle fibers and could benefit from progressive loading with NAVA to exercise their diaphragm and prepare them for possible extubation.

Future large size randomized controlled trials should be established to compare NAVA with volume targeted and pressure controlled ventilation in newborns with mature respiratory drive. Future studies should also compare NIV NAVA and biphasic CPAP or high flow nasal cannula to demonstrate if NIV-NAVA can prevent endotracheal intubation without causing abdominal distension or increasing the rate of necrotizing enterocolitis. As most previous studies and trials were not sufficiently large and did not include long-term patient oriented outcomes, multicenter, randomized, outcome trials are needed to determine whether NAVA is effective in avoiding intubation, facilitating extubation,

decreasing time of ventilation, reducing the incidence of CLD, decreasing length of stay, and improving long-term outcomes such as the duration of ventilation, length of hospital stay, rate of pneumothorax, CLD and other major complications of prematurity.

In order to prevent barotrauma, we recommend that the next generations of NAVA equipment for neonatal use should enable automatic setting of ventilatory parameters in the backup PC mode based on the values generated by NAVA. We believe that they should also include an upper limit to the IT as in conventional ventilation and that the manufacturers of Edi catheters should make smaller sizes available for extreme low birth weight infants. We also recommend that newly developed NAVA ventilators also include leak compensation, high frequency ventilation option as well as a peripheral flow sensor because it is essential for all modes of conventional ventilation as well as NAVA.

CONCLUSION

NAVA ventilation utilizes the patient's neural respiratory drive to synchronize ventilatory support on a breath-by-breath basis based on the infant's ongoing needs. It allows preterm neonates to use physiologic feedback to control ventilation and enhance comfort for each breath. The Edi signal provides the clinician with previously inaccessible information about central respiratory drive useful for both weaning and diagnostics, with infants informing the neonatologist of what support they need, directing both the timing and depth of their breathing pattern. NAVA appears to work well in neonates but if it makes a difference in outcomes in this population has not been established so far. The remaining challenge for neonatal health care providers is the steep and prolonged learning curve for the application of NAVA.

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