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Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis

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Abstract Purpose: Neurally adjusted ventilatory assist (NAVA) is a mode of ventilation designed to improve patient–ventilator interaction by interpreting a neural signal from the diaphragm to trigger a supported breath. We hypothesized that neurally triggered breaths would reduce trigger delay, ventilator response times, and work of breathing in pediatric patients with bronchiolitis. **Methods:** Subjects with a clinical diagnosis of bronchiolitis were studied in volume support (pneumatic trigger) and NAVA (pneumatic and neural trigger) in a crossover design. Airway flow and pressure waveforms were obtained with a pneumotachograph and computerized digital recorder and were recorded for 120 s for each experiment. **Results:** Neurally triggered breaths had less trigger delay (ms) (40 ± 27 vs. 98 ± 34 ; $p < 0.001$) and reduced ventilator response times (ms) (15 ± 7 vs. 36 ± 25 ; $p < 0.001$) compared with pneumatically triggered breaths. Neurally triggered breaths had

reduced pressure–time product (PTP) area A ($\text{cmH}_2\text{O} \cdot \text{s}$), the area of the pressure curve from initiation of breath to start of ventilator pressurization (0.013 ± 0.010 ; $p < 0.001$), and reduced PTP area B ($\text{cmH}_2\text{O} \cdot \text{s}$), the area of the pressure curve from start of ventilator pressurization to return of baseline pressure (0.008 ± 0.006 vs. 0.023 ± 0.009 ; $p = 0.003$). Reduced PTP may indicate decreased work of breathing. **Conclusion:** Neurally triggered breaths reduce trigger delay, improve ventilator response times, and may decrease work of breathing in children with bronchiolitis. Further analysis is required to determine if neurally triggered breaths will improve patient–ventilator synchrony.

Keywords Mechanical ventilation · Neurally adjusted ventilatory assist · Trigger delay · Work of breathing · Patient–ventilator interaction

Introduction

Patient inspiratory effort to trigger the ventilator comprises 10–30% of total breathing effort. Trigger delay directly correlates with respiratory drive (the more time in the trigger phase, the more respiratory effort required to trigger the ventilator) [1]. The pre-trigger/trigger phase of a breath consists of a patient effort or trigger delay (the

time between the start of patient effort and the beginning of ventilator pressurization) and the response time of the ventilator (time between the beginning of ventilator pressurization and the return of pressure to baseline). Neurally adjusted ventilatory assist (NAVA) is a Food and Drug Administration (FDA)-approved mode of ventilation that captures electrical signals from the diaphragm allowing a patient to control both when the ventilator

provides a breath and how much assistance they receive [2]. NAVA interprets a neural signal from the patient's diaphragm to trigger a supported breath rather than a pneumatic signal from the patient's airway [3]. Since NAVA is triggered by a signal from the patient's diaphragm and is not dependent on a pneumatic airway signal, there should theoretically be a shorter trigger delay and reduced response time of the ventilator. Earlier studies using NAVA support this rationale [4, 5]. Comparing pressure support ventilation to NAVA in rabbits demonstrated that increasing levels of pressure support beyond 8 cmH₂O caused increased work of breathing. However, with increasing NAVA support, there was little effect on trigger and cycling-off delays and no wasted inspiratory efforts [4]. The same was true in 14 adult patients with acute respiratory failure where similar airway pressures in NAVA had reduced trigger delays compared with pressure support [5].

Patient effort is actually greater when the patient does not meet the ventilator trigger threshold than when the trigger threshold is reached. At high levels of assistance, up to a third of a patient's inspiratory effort may not trigger the machine. Ineffective breaths have higher tidal volumes and shorter expiratory times than effective breaths, which leads to increased intrinsic positive end-expiratory pressure (PEEP), more asynchrony, and increased work of breathing [6]. By using a neural trigger and subsequently reducing ventilator response time, patient work of breathing will therefore be reduced.

While there are studies demonstrating safety [7, 8] with use of NAVA in pediatric patients, there are no studies in pediatric patients that specifically examine the effects of neurally triggered breaths on trigger delay, ventilator response time, or work of breathing. We hypothesize that neurally triggered breaths will reduce trigger delay and ventilator response time in mechanically ventilated pediatric patients with bronchiolitis. The reduction in trigger delay and ventilator response time will decrease work of breathing.

Methods

The study was conducted from January 2009 to February 2010 in the Pediatric Intensive Care Unit (PICU) at Arkansas Children's Hospital, Little Rock, Arkansas. The institutional review board approved the study. Informed consent was obtained from the parents of all infants prior to study enrollment.

Pediatric patients aged 0–24 months with respiratory failure requiring mechanical ventilation with a clinical diagnosis of bronchiolitis were eligible for the study. A diagnosis of bronchiolitis was confirmed if a patient met the following clinical criteria: history of cough or wheeze and presence of at least two signs of respiratory distress

including nasal flaring, tachypnea, subcostal retractions, suprasternal retractions, use of auxiliary muscles, auscultation of lungs with predominance of wheezing or prolonged expiration. Chest x-ray findings were consistent with pulmonary hyperinflation and had absence of lobar consolidation [9]. Mechanical ventilation was initiated at the discretion of the attending physician for hypercapnia, respiratory acidosis, fatigue, or apnea. Patients were enrolled after informed consent was obtained; however, the study was not performed until the patients were in the weaning phase of mechanical ventilation [PEEP < 10, volume support ventilation mode, fraction of inspired oxygen (FiO₂) ≤ 50%, pulse oximetry ≥ 92%].

The following information was documented for each participant: PICU admission/discharge dates, hospital admission/discharge dates, length of ventilation. Demographic information was also collected: date of birth/age (months), sex, race, weight (kg), and diagnosis.

Patients were excluded if they had not yet reached 36 weeks gestational age, had evidence of chronic lung disease (oxygen requirement at baseline, need for chronic diuretics and/or inhaled respiratory treatments), cardiac disease, hemodynamic instability (requiring vasopressors or a fluid bolus for hypotension in previous 24 h), neuromuscular disease, or tracheostomy. All patients had a modified NAVA nasogastric (NG) tube placed; any patient with a contraindication to NG tube placement [basilar skull fracture, choanal atresia, nasal surgery within 3 months, or significant coagulopathy (platelets <50,000, oozing from IV sites)] was excluded.

All participants were sedated per attending physician recommendations. At the time of the study, the level of sedation was documented using the COMFORT scale [10]. Before each experiment started, the participant was reassessed for pain and agitation to maintain him at a COMFORT scale rating of 8–26, which corresponds to both deep and light sedation.

Participants had a modified (with mounted micro-electrodes) FDA-approved NAVA NG tube placed in their esophagus. Placement of the modified NG tube for optimal Edi (diaphragm electrical) signal was verified using the Edi catheter positioning screen on the Servo *i* ventilator (Maquet, Bridgewater, NJ). The occlusion method was also used to confirm accurate placement of the NG tube [11].

Participants were ventilated with the Servo *i* ventilator in both volume support (VSV) and NAVA in a prospective, crossover design. Study order (whether VSV or NAVA was tested first) was randomized by computer. Ventilator settings for VSV were determined by the attending physician (who did not participate in the study) and were not changed for the purpose of the study. PEEP and FiO₂ were kept the same in both VSV and NAVA modes. The NAVA level was adjusted to deliver the same tidal volume as was set in VSV. There was a 10-min

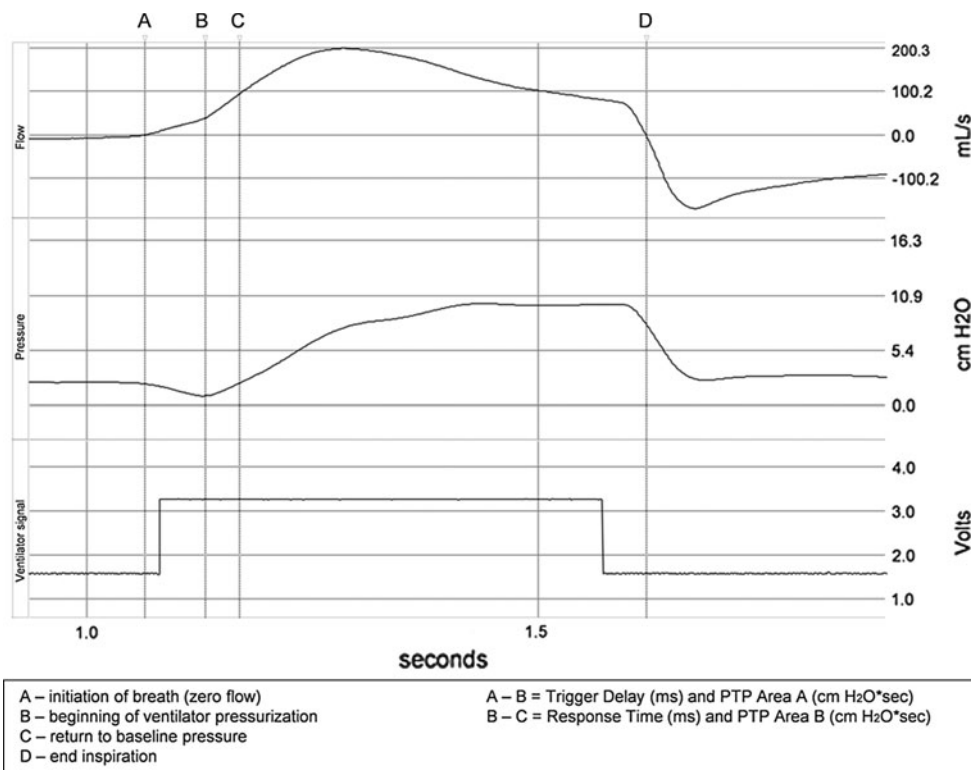
minimum wait time between the two experiments to allow the subject time to acclimate to the change in ventilator mode. At study completion, ventilator settings were changed back to those previously determined by the attending physician prior to start of the study. The modified NG tube was left in place.

Measurements of respiratory flow and pressure waveforms were acquired using the Biopac MP-100 System (Biopac Systems, Inc., Santa Barbara, CA). A heated 0–35 L/min pneumotachograph (PNT) (Hans Rudolph Inc., Shawnee, KS) was placed in-line, at the patient wye, between the endotracheal tube and the patient ventilator circuit. Dead space associated with the PNT was 8.74 mL. Flow was calibrated using a flow meter. Volume measurements were obtained through the computer by integrating the flow signal. Volume was verified with a calibrated syringe (Hans Rudolph, Inc., Kansas City, MO). To monitor pressure, the PNT was equipped with a pressure hose, barb-type port that allowed airway pressure sampling. Pressure was calibrated with a manometer. The ventilator trigger signal is an electronic signal acquired from the ventilator controller that corresponds to the opening and closing of the inspiratory valve. All output signals were routed via an analog channel box into the Biopac MP100 data acquisition unit converting them into digital signals that could then be processed by a computer. Signals were obtained at a rate of 1,000 samples per second. Data was collected for 120 s for each mode. Breaths collected with the PNT at

the airway were matched time-wise with breaths displayed (via video recording the Servo *i* screen) and data downloaded from the Servo *i* ventilator.

Two of our primary outcomes were trigger delay and ventilator response time. Flow and pressure waveforms obtained with the PNT at the airway were analyzed for these two outcomes. Trigger delay was defined as the time interval (ms) from initiation of a breath (zero flow) to the beginning of ventilator pressurization (most negative deflection of pressure). Trigger delay reflects patient effort. Ventilator response time was defined as the time interval (ms) from the beginning of ventilator pressurization (most negative deflection of pressure) to return to baseline pressure. Ventilator response time reflects the response of the ventilator to patient effort. The other primary outcome was pressure–time product (PTP). A tension–time index or PTP is reflective of work of breathing. PTP area A was defined as the area of the pressure curve (integration of pressure with respect to time) from initiation of a breath (zero flow) to the beginning of ventilator pressurization (most negative deflection of pressure). PTP area A reflects patient work of breathing. PTP area B was defined as the area of the pressure curve (integration of pressure with respect to time) from the beginning of ventilator pressurization (most negative deflection of pressure) to return to baseline pressure. PTP area B reflects both patient and ventilator work of breathing. A graphical depiction of this explanation can be seen in Fig. 1.

Fig. 1 Flow versus time (*top*) and pressure versus time (*middle*) tracings of one breath, illustrating how trigger delay, response time, PTP area A, and PTP area B were measured for each breath



For each study utilizing VSV, ten consecutive breaths were analyzed for trigger delay, ventilator response time, PTP area A, and PTP area B. All VSV breaths were pneumatic triggered breaths. For each study utilizing NAVA, 20 breaths were analyzed for trigger delay, ventilator response time, PTP area A, and PTP area B. NAVA mode breaths can be pneumatic triggered or neural triggered. We analyzed ten consecutive pneumatic breaths and ten consecutive neurally triggered breaths for each participant, when available. Breathes were measured consecutively unless a breath was determined to not be a true representation (i.e., evidence of movement, double trigger, etc.) of the majority of the breaths in the sequence. If the breath was determined to not be a true representative breath of the sequence, it was skipped and the next available breath in the time sequence was analyzed. Because the type of trigger for each breath was dependent on the patient, there were not always ten pneumatic and ten neural triggered breaths for each participant. We analyzed what was available with the goal being ten pneumatic triggered and ten neural triggered for each participant. Classification of breaths was determined via video recording of the screen of the Servo *i* during experiments. Trigger indication is displayed in the message/alarm field of the screen of the Servo *i* and is displayed as a pneumatic or neural trigger for each breath. Breathes from the video recording of the Servo *i* screen were matched time-wise to breaths collected from the PNT at the airway opening and documented as pneumatic or neural triggered.

To incorporate the repeated measures taken from each participant, we took the mean of ten breaths (if available) for each participant, ventilator mode, and type of trigger (pneumatic and neural). Means were compared using a paired *t* test. $P < 0.05$ was considered significant. NAVA mode neural trigger was compared to NAVA mode pneumatic trigger and to VSV mode pneumatic trigger breaths. In addition, NAVA mode pneumatic trigger was compared to VSV mode pneumatic trigger breaths. Data analyses were constructed using SPSS© version 14.0 for Windows, SPSS Inc., Chicago, IL.

Results

A total of 52 subjects were screened, and 30 subjects were enrolled in the study. Six families declined consent and 16 subjects did not meet inclusion criteria. Six of the enrolled subjects did not complete the study (5 subjects were extubated before the study could be performed and 1 patient was not studied because the computer system failed prior to study start). Of the 24 subjects that did complete the study, one subject's data was excluded because of PNT failure. Four subjects completed only the VSV portion of the study because an Edi signal could not be obtained to

Table 1 Demographic data

	<i>n</i> (%)
Sex	
Males	12 (52.2)
Females	11 (47.8)
Race	
White, non-Hispanic	12 (52.2)
Hispanic	5 (21.7)
African American	4 (17.3)
Other	2 (0.09)
Primary diagnosis	
RSV bronchiolitis	14 (60.8)
Apnea	5 (21.7)
Bronchiolitis	4 (17.3)
	Mean ± SD
Age (months)	1.6 ± 1.0
Weight (kg)	4.2 ± 1.4
Pulse Ox saturation (%)	97 ± 2
Heart rate (bpm)	142 ± 15
Temperature (°C)	36.5 ± 0.6
Blood pressure—systolic (mmHg)	90 ± 15
Blood pressure—diastolic (mmHg)	53 ± 11
Total days in hospital	21 ± 11
Total days in PICU	12 ± 6
Total days on ventilator	9 ± 5
Sedation scale	
Pre-NAVA mode	20 ± 3
Pre-VS mode	20 ± 3

Total *n* = 23

do the NAVA portion of the study. A total of 19 subjects completed both arms of the study, but VSV data was analyzed for all 23 patients that completed the VSV part of the study.

The mean age was 1.6 ± 1.0 months and the mean weight was 4.2 ± 1.4 kg. Other demographic data are shown in Table 1. There were no significant adverse events, and no patients died.

As shown in Fig. 2, neurally triggered breaths had significantly less trigger delay (ms) when compared with pneumatically triggered breaths in both VSV and NAVA ($p < 0.001$). Ventilator response times (ms) were also significantly improved with neurally triggered breaths compared with pneumatically triggered breaths in both modes ($p < 0.001$). Neurally triggered breaths had reduced PTP area A ($\text{cmH}_2\text{O} \cdot \text{s}$), the area of the pressure curve from initiation of breath to start of ventilator pressurization. PTP area B ($\text{cmH}_2\text{O} \cdot \text{s}$), the area of the pressure curve from start of ventilator pressurization to return of baseline pressure, was also reduced with neurally triggered breaths.

Discussion

Our results demonstrate that in infants with bronchiolitis, neurally triggered breaths have less trigger delay and improved ventilator response time compared with

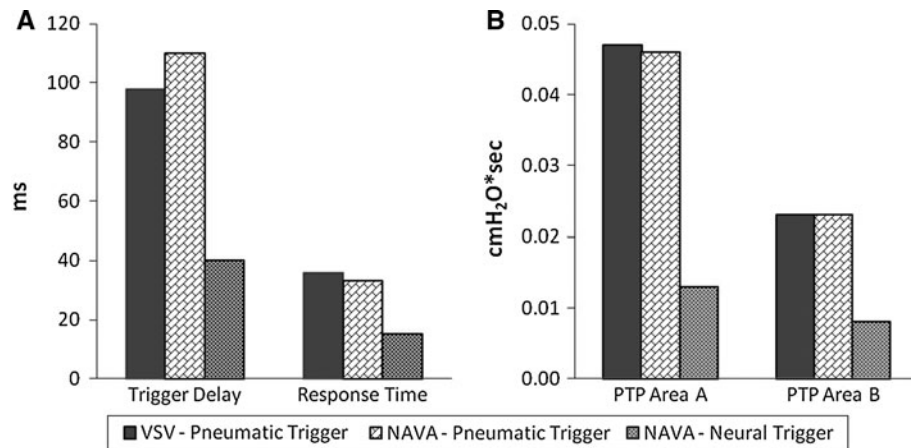


Fig. 2 Mean values for trigger delay, ventilator response time, PTP area A, and PTP area B for each type of trigger. **a** Neurally triggered breaths had less trigger delay (ms) (40 ± 27 vs. 98 ± 34 ; $p < 0.001$) and reduced ventilator response times (ms) (15 ± 7 vs. 36 ± 25 ; $p < 0.001$) compared with pneumatically triggered breaths. **b** There was reduced PTP area A (cmH₂O*s), the area of the pressure curve from initiation of breath to start of ventilator

pressurization (0.013 ± 0.010 ; $p < 0.001$), and PTP area B (cmH₂O*s), the area of the pressure curve from start of ventilator pressurization to return of baseline pressure (0.008 ± 0.006 vs. 0.023 ± 0.009 ; $p = 0.003$). These values suggest decreased work of breathing for neurally triggered breaths. Comparisons between the two types of pneumatic trigger for all outcomes were not significant

pneumatically triggered breaths. Also, neurally triggered breaths may lead to decreased work of breathing, as evidenced by decreased PTP of areas A and B. This is the first clinical study that uses NAVA in a specific population of infants with lung injury.

Our findings of decreased trigger delay are similar to earlier studies in both animal models and patients. In rabbits with acute lung injury, trigger delay increased more with increasing levels of pressure support than with increasing levels of NAVA [12]. In a population of pediatric patients (mostly with cardiac disease), Breatnach et al. [8] concluded that NAVA mode offered superior synchrony to pressure support ventilation (PSV) as there was faster triggering with neurally triggered breaths. In adult patients with chronic obstructive pulmonary disease (COPD), Spahija et al. [13] also found greater trigger delays with PSV compared with NAVA. The average trigger delay in their study for both types of trigger was twice the delay in our study; however, their population of patients with COPD has inherent tendencies to higher trigger delay related to their disease process. The group also used a different method for measuring trigger delay. They defined trigger delay as the time difference between the start of the diaphragm electrical signal and the onset of ventilator inspiratory flow. We were unable to use this definition as we did not have the capability to integrate the diaphragm signal into our software until halfway through patient enrollment. Despite the absolute differences in trigger delay and differences in methodology, the results are similar. Spahija showed an approximate 50% reduction in trigger delay with neurally triggered breaths, and we showed a 60% reduction.

There are no other studies that look specifically at ventilator response time, but there are other studies that examine the effect of neurally triggered breaths on work of breathing. In rabbits with acute lung injury, the addition of PEEP to NAVA appears to unload respiratory muscles by increasing phasic activation of the diaphragm [14]. In healthy patients, NAVA relieves inspiratory muscle workload during maximal inspirations in both invasive [15] and noninvasive ventilation [16]. In adults with acute respiratory failure, increases in NAVA level increased breathing variability and complexity, which the authors suggest is a sign of progressive respiratory system unloading [17].

We did not directly measure work of breathing in this study. None of the previously mentioned studies use the PTP of areas A and B as their indicator of work of breathing. However, Spahija [13] used the PTP of the diaphragm in the triggering phase and found lower PTP in NAVA compared with PSV. PTP estimates the metabolic cost of breathing and quantifies inspiratory effort [18–21]. PTP also gives a better indication of energy expenditure of the respiratory muscles because it evaluates energy expenditure during both isometric and nonisometric contraction [19, 22]. Our statistically significant reduction in PTP of areas A and B therefore strongly suggests that neurally triggered breaths have reduced inspiratory effort and energy expenditure, which likely decreases overall work of breathing.

There are additional limitations to our study. The literature has thus far only compared NAVA to PSV, which is logical because PSV is the backup mode of ventilation should a diaphragm electrical signal not be detected when using NAVA. All of our subjects were studied in VSV

because that is the standard mode of ventilation used for weaning in our institution. We also only allowed a 10-min acclimation period when the mode of ventilation was changed prior to the 2-min study period. Perhaps a longer duration of time would have allowed for more improved acclimation to a new mode. There was also a learning curve in performing the experiments and in achieving correct NAVA NG tube placement. We had three patients in whom we could not obtain an Edi signal. In an adult study, correct NAVA NG catheter placement was obtained in all patients either by measurement described in the package insert or by ventilator screen tools [23]. There is not any data for the success of correct NG placement in pediatric patients.

The clinical implications from this study are important. On the basis of our results, a baby breathing 60 times/min spends 10% of the breath cycle in the trigger phase for pneumatically triggered breaths, versus 4% of the breath cycle for neurally triggered breaths. This equates to a 60% decrease in the amount of time spent triggering the ventilator. Improvements in trigger delay

should therefore lead to improved patient-ventilator synchrony, the presence of which can lead to ventilation-perfusion mismatch, increased work of breathing [24], respiratory muscle injury, prolonged ventilator weaning, increased length of hospital stay, and higher costs [25].

Conclusion

Neurally triggered breaths have less trigger delay and improved ventilator response times. They also have decreased PTP area A and area B, which suggests decreased work of breathing. Further study is required to demonstrate if these differences will improve patient-ventilator synchrony.

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