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ORIGINAL ARTICLE

Evaluating peak inspiratory pressures and tidal volume in premature neonates on NAVA ventilation

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Abstract

Neurally adjusted ventilatory assist (NAVA) ventilation allows patients to determine their peak inspiratory pressure and tidal volume on a breath-by-breath basis. Apprehension exists about premature neonates' ability to self-regulate breath size. This study describes peak pressure and tidal volume distribution of neonates on NAVA and non-invasive NAVA. This is a retrospective study of stored ventilator data with exploratory analysis. Summary statistics were calculated. Distributional assessment of peak pressure and tidal volume were evaluated, overall and per NAVA level. Over 1 million breaths were evaluated from 56 subjects. Mean peak pressure was 16.4 ± 6.4 in the NAVA group, and 15.8 ± 6.4 in the NIV-NAVA group (*t* test, $p < 0.001$). Mean tidal volume was 3.5 ± 2.7 ml/kg.

Conclusion:In neonates on NAVA, most pressures and volumes were within or lower than recommended ranges with pressure-limited or volume-guarantee ventilation.

What is known:
- *Limiting peak inspiratory pressures or tidal volumes are the main strategies to minimize ventilator-induced lung injury in neonates. Neurally adjusted ventilatory assist allows neonates to regulate their own peak inspiratory pressures and tidal volumes on a breath-to-breath basis using neural feedback.*

What is new:
- *When neonates chose the size of their breaths based on neural feedback, the majority of peak inspiratory pressures and tidal volumes were within or lower than the recommended peak inspiratory pressure or tidal volume ranges with pressure-limited or volume guarantee ventilation.*

Keywords Neurally adjusted ventilatory assist (NAVA) · Premature neonates · Ventilatory induced lung injury · Tidal volume · Peak pressure

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Abbreviations

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
Edi	Electrical activity of the diaphragm
NAVA	Neurally adjusted ventilatory assist
NIV NAVA	Non-invasive NAVA
PIP	Peak inspiratory pressure
PS	Pressure support
VT	Tidal volume
VTV	Tidal volume ventilation

Introduction

Despite advancements in neonatal ventilation modalities, premature neonates remain at significant risk for bronchopulmonary dysplasia (BPD) [1]. When compared to

pressure-limited ventilation, the use of volume-targeted ventilation has been associated with more favorable outcomes [2]. Data for selecting the appropriate target tidal volume (VT) for specific patients with different clinical conditions are limited [3]. Typical VT ranges to initiate tidal volume ventilation (VTV) range from 4 to 7 ml/kg [3, 4].

Neurally adjusted ventilatory assist (NAVA) ventilation allows patients to control their own peak inspiratory pressure (PIP) and VT on a breath-to-breath basis. The patient controls the amount of pressure delivered by the ventilator using the electrical activity of the diaphragm (Edi) waveform to trigger-on and cycle-off each assisted breath, therefore providing truly synchronized ventilation [5]. This Edi signal is obtained from a specialized indwelling nasogastric feeding tube with embedded sensing electrodes (NAVA catheter). When properly positioned, it can accurately and reliably trigger and cycle the ventilator breath, independent of airway leaks, making it ideal for synchronizing non-invasive ventilation [6].

Studies have shown that neonates, while in both invasive and non-invasive NAVA, have the ability to "switch-off" neural inspiration, and then cycle-off the ventilator when an appropriate volume/pressure has been reached [7, 8]. By optimally supporting native breathing reflexes, NAVA can facilitate patient effort in a synchronous fashion [6]. Despite NAVA's neuro-ventilatory coupling advantage that NAVA ventilation provides, concern has been raised that enabling premature neonates to choose their own ventilator parameters could result in excessively high PIPs and VTs, theoretically increasing the risk of pneumothorax acutely, and chronic lung disease over the long term [9]. We therefore planned to evaluate the range of PIP and VT that premature neonates generate while on NAVA.

Methods

This was a retrospective study of neonates that were clinically stable on invasive and non-invasive (NIV) NAVA ventilation and had data downloaded from the Servo-i (version 6.01, Getinge, Germany). IRB approval was obtained, and consent was waived. Data collected included PIP, expiratory VT, and NAVA level. These were all measured in the ventilator without a proximal sensor. The data were then sorted into PIP ranges in blocks of 5 cmH_2O from 5 to 9.99 to 30–35 cmH_2O. Expiratory VT was normalized to study weight and sorted into VT ranges from 0 to 0.9 to 9–9.99 ml/kg. The data were also evaluated for each NAVA level. Data were not included during the times the patient was in NAVA Pressure Support (PS) or in backup (pressure control) because these levels were set by the care provider.

Statistical methods

Examination of data included calculation of summary statistics for continuous data, along with frequencies and percentages for categorical data. Based on clinical rationale, each observation is viewed as independent; therefore, the statistical analysis was conducted on the full set of observations. Data were recorded separately for each variable without time stamps and subjects had variable numbers of observations for P-Peak and VT; therefore, the P-Peak values and the VT values could not be linked by observation. The independent samples *t* test was conducted to assess for potential difference in overall PIP by group (NIV-NAVA vs. NAVA). A factorial ANOVA was conducted to assess for potential differences in PIP by main effects of group and NAVA level as well as their interaction. Post hoc pairwise testing with Tukey adjustments was done to control for type I error rate. The χ^2 Mantel-Haenszel Trend Test was used to assess and describe the potential relationships of NAVA levels with group, $PIP_{(quartiles)}$, and $VT_{(quartiles)}$. The chi-square test of independence was used to assess the relationship between group and NAVA level, followed by the chi-square test for trend to assess for evidence of trends of VT and PIP by NAVA level in both the NAVA and NIV-NAVA groups. Statistical analyses were completed using SAS 9.4/14.2©. Unless otherwise noted, all testing was two-tailed and evaluated at the type I error rate of alpha = 0.05 level of statistical significance.

Results

Twenty-seven subjects underwent data collection for PIP and VT on invasive NAVA. Circuit compliance was turned off on one subject, leaving only twenty-six subjects with reportable tidal volume data. Average birth weight was 857 ± 362 g (range 380 to 2055 g). The subjects weighed 862 ± 361 g (range 500 to 2040 g) at the time of data collection. Average gestational age was 26.5 ± 2.3 weeks (range 24 weeks to 33 weeks) and their average age at the time of data collection was 8 ± 9 days (range 1 to 36 days). Eighty three percent of the subjects were exposed to maternal steroids and 96% received postnatal surfactant. Neonatal diagnoses as the reason for ventilation during the study were respiratory distress syndrome (75%), chronic pulmonary insufficiency of prematurity (21%), and pneumonia (4%). All subjects were on caffeine. During this download period, no pneumothoraces or other adverse events were reported.

Twenty-nine subjects underwent data collection on NIV NAVA. Average birth weight was 835 ± 179 g (range 490 to 1060 g). The subjects weighed 844 ± 165 g (range 655 to 1220 g) at the time of data collection. Average gestational age was 26.8 ± 1.5 weeks (range 24 to 29 weeks) and their average age at the time of data collection was 13 ± 12 days

(range 2 to 38 days). Ninety two percent were exposed to maternal steroids and 33% received postnatal surfactant. Neonatal diagnoses as the reason for ventilation during the study were respiratory distress syndrome (67%), chronic pulmonary insufficiency of prematurity (25%), and pneumonia (8%). All subjects were on caffeine. During this download period, no pneumothoraces or other adverse events were reported.

Outcomes of these subjects include a mortality of 6% (VON median 15.1%), pneumothorax 6% (VON median 4.1%), and BPD 27% (VON median 27.1%). However, many of these babies were on multiple modes of ventilation throughout their (sometimes prolonged) hospital courses and outcomes should be interpreted with caution. Importantly, these outcomes are not worse than the VON data.

Baseline NAVA and NIV-NAVA settings were NAVA levels that ranged from 0.5–4.0 cmH_2O/mcV, PEEP 5 cmH_2O, apnea times 3–5 s, PIP limit 35–40 cmH_2O (which limits the PIP to 5 cmH_2O below the PIP limit), and variable backup settings determined by the treating physician. All settings, except NAVA level and F_IO_2 were constant throughout the data collection period.

There were 27 subjects in the NAVA group with 481,949 observations of P-Peak, and 26 subjects with 412,661 observation of VT. There were 29 subjects in the NIV-NAVA group with 540,386 observations of P-Peak. Table 1 shows the number of breaths at each NAVA level.

Figure 1 shows the breath-to-breath variability in PIP and expiratory VT with slower changes in respiratory rate in a typical tracing from a subject. This 1-min tracing shows that PIP mostly varied between 15 and 20 cmH_2O with one breath as low as 12 cmH2O and one at 24 cmH_2O. VT mostly varied between 2 and 5 ml/kg with few VT less than 1 ml/kg and a few (4/60) as high as 8 ml/kg.

The distribution of VT and PIP for a typical subject on NAVA and PIP for a typical subject on NIV NAVA are shown in Fig. 2. The subject on NAVA had a median VT of 3.7 (IQR 2.1, 5.6) ml/kg with a range of 0.3–9.8 ml/kg and a median PIP of 14 (IQR 11, 17) cmH_2O with a range of 7 to 30 cmH_2O. The subject on NIV NAVA had a median PIP of 12 (IQR 11, 14) cmH_2O with a range of 7 to 31 cmH_2O.

Table 1 Number and distribution of breaths at each NAVA level analyzed on NAVA and NIV NAVA

NAVA level	PIP NAVA	PIP NIV NAVA	VT NAVA
0.5	841	114	780
1.0	99,712	63,326	65,333
1.5	233,079	259,557	176,988
2.0	70,472	95,163	52,515
2.5	69,577	120,198	51,627
3.0	8033	2028	7548
3.5	108	0	56
4.0	127	0	68
Total	481,949	540,386	412,661

Figure 3 shows the PIP distribution on NAVA and NIV NAVA. The mean PIP was 16.4 ± 6.4 (range 5.2–41.1) in the NAVA group, and 15.8 ± 6.4 (range 4.2–35.1) in the NIV-NAVA group (*t* test: *p* value < 0.001). The median PIP on NAVA was 14.9 cmH_2O (IQR 11.4–20) and on NIV NAVA was 13.7 cmH_2O (IQR 10.9–19). The upper graph, panel A, shows the % PIP distribution on invasive NAVA. Seventy eight percent of breaths were at a PIP < 20 cmH_2O and only 3% of breaths had PIP ≥ 30 cmH_2O. The lower graph, panel B shows the % PIP distribution on NIV NAVA. Seventy nine percent of breaths were at a PIP < 20 cmH_2O and only 4.5% of breaths had PIP ≥ 30 cmH_2O. PIP was different by NAVA level and group (factorial ANOVA: *p* value < 0.001 for model and interaction of NAVA level with group); post hoc testing with Tukey adjustments to control type I error rate provides evidence for pairwise mean differences. The effect of group on PIP was dependent upon the level of NAVA. Figure 4 a and b graphically depict the distribution of PIP by NAVA level.

Figure 5 shows the % expiratory VT distribution on invasive NAVA. The average VT was 3.5 ± 2.7 ml/kg (range 0.1–10 ml/kg) and the median was 2.9 ml/kg (IQR 1.5–5.2). Seventy-eight percent of breaths were at a VT < 4 ml/kg and only 5% of breaths had VT > 7 ml/kg. Figure 6 graphically depicts the distribution of VT by NAVA level. A dependent relationship between group and NAVA level was observed (1-way ANOVA: *p* value < 0.001) and post hoc pairwise testing with Tukey adjustments to control type I error rate provides evidence that means were different between pairs: 0.5 VS 1.0, 1.0 VS 1.5, 1.5 VS 2.0, 2.0 VS 2.5, and 3.0 VS 3.5.

To further examine for potentially significant trends, ordered categorical variables were created for VT and PIP by using threshold values from 25th, 50th, and 75th percentiles to categorize each observation by quartile. There was significant trend effect with VT and NAVA level in the NAVA group as well as PIP and NAVA level in both the NAVA and NIV-NAVA groups (chi-square test for trend: *p* value < 0.001 for each). In other words, as the NAVA level increases, so does the $VT_{(quartile)}$/$PIP_{(quartile)}$ level. Examination of proportions indicates that even at the highest quartile of VT or P-Peak, low percentages of subjects were at a high NAVA level with approximately 97% at level 2.5 or below.

Discussion

This study provides the first data of PIPs and VTs of preterm neonates while on invasive and NIV-NAVA. These data are predominantly lower than the accepted range for both PIP and

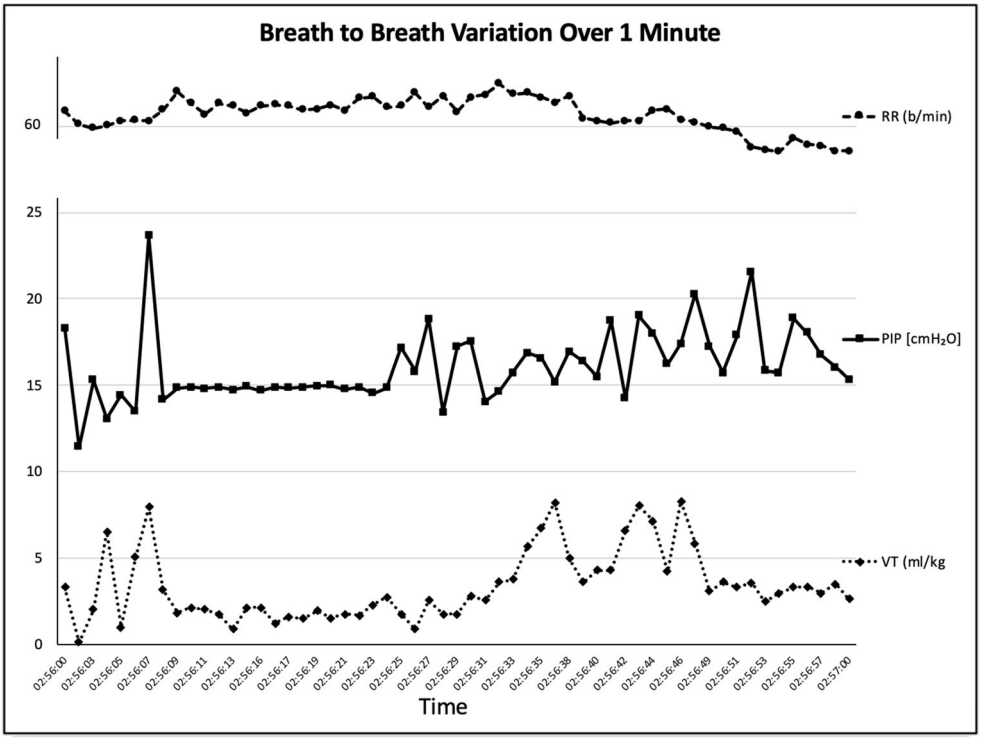

Fig. 1 One-minute tracing from a 26-week, 960-g subject at 30 days, 1360 g with chronic pulmonary insufficiency of prematurity. PIP mostly varied between 15 and 20 cmH_2O with one breath as low as 12 cmH2O and one at 24 cmH_2O. VT mostly varied between 2 and 5 ml/kg with few VT less than 1 ml/kg and a few as high as 8 ml/kg. Despite these wide variations in PIP and VT, there was minimal variation in respiratory rate

VT in neonates and suggest that premature neonates have functionally mature respiratory control and feedback mechanisms. Previous studies have shown that PIP and VT on NAVA was lower than on conventional ventilation but these studies assessed average values during the study period and did not look at the range and distribution of individual breaths [10–13].

Guidelines for the use of pressure-limited ventilation in neonates are limited [4, 14]. According to the Handbook for Neonatal Intensive Care, the recommendations for starting pressures for beginning ventilator support are PIPs of 16–20 cmH_2O [15]. However, there are no evidence-based studies to support these guidelines. A cross-sectional study of 173 European NICUs reported an average PIP range of 15–25 cmH_20 in preterm neonates [4]. In a study to investigate the effects of triggered and untriggered inflations on PIP in neonates, triggered inflations had a PIP of 12.9 ± 4.9 cmH_2O vs. untriggered of 17.0 ± 3.3 cmH_2O [16]. Some authors have

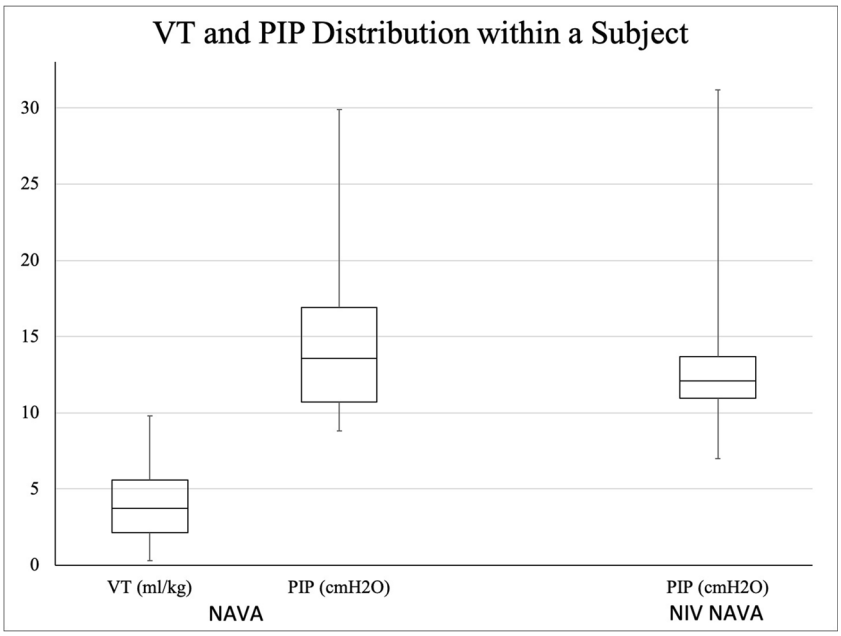

Fig. 2 Distribution of VT and PIP on NAVA (17,912 breaths) and PIP on NIV NAVA (20,164 breaths). The subject on NAVA was a 25-week, 669-g neonate at 24 days and 670 g with chronic pulmonary insufficiency of prematurity was analyzed. The subject on NIV NAVA was a 27-week, 795-g neonate at 4 days and 740 g with respiratory distress syndrome. The data are median with IQR and the whiskers are the minimum and maximum values

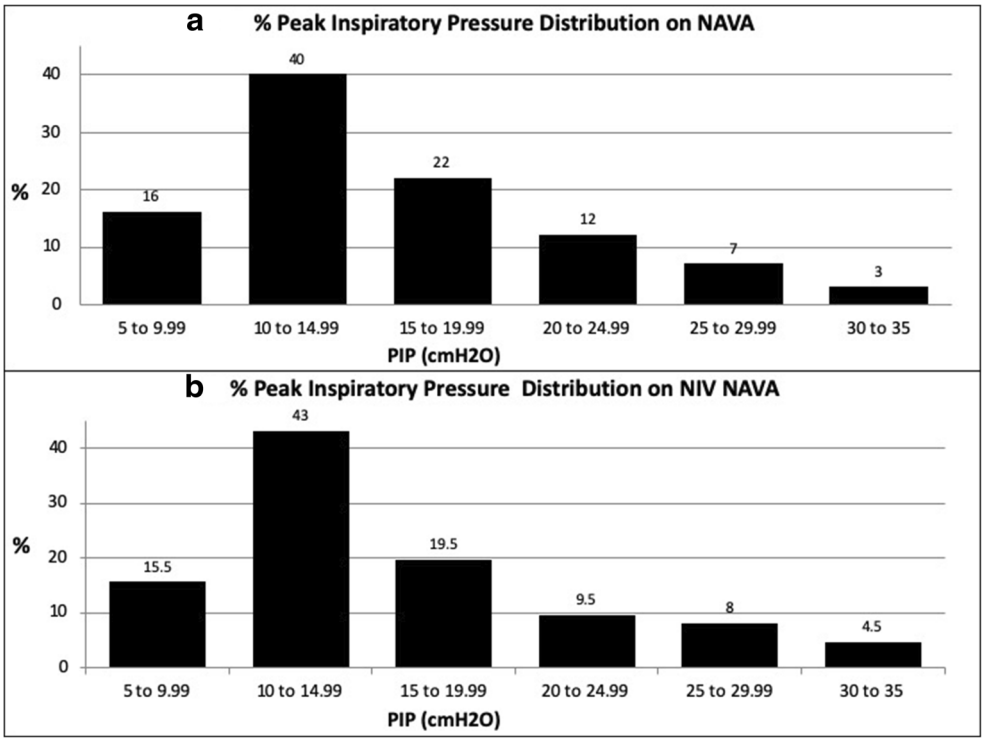

Fig. 3 **a** Percent breath distribution for PIP in 5 cmH_2O increments on invasive NAVA. **b** Percent breath distribution for PIP in 5 cmH_2O increments on NIV NAVA

suggested keeping PIP below 20 cmH_2O but do not provide data to support these recommendations [17]. In animal studies, PIPs > 30 cmH_2O have been shown to produce lung injury in relatively short periods. One study in sheep showed that as few as five high PIP breaths delivered immediately after birth could produce diffuse alveolar damage and hyaline membrane formation [18]. Other studies in rats and piglets looked at lung damage from ventilation with a high PIP from 20 min to 48 h [19, 20]. At a typical ventilator rate of 40 breaths per minute, these animals were exposed to 800 to 57,600 continuous breaths at those pressures [20]. The vast majority of PIPs from our study were less than 20 cmH_2O and only a small

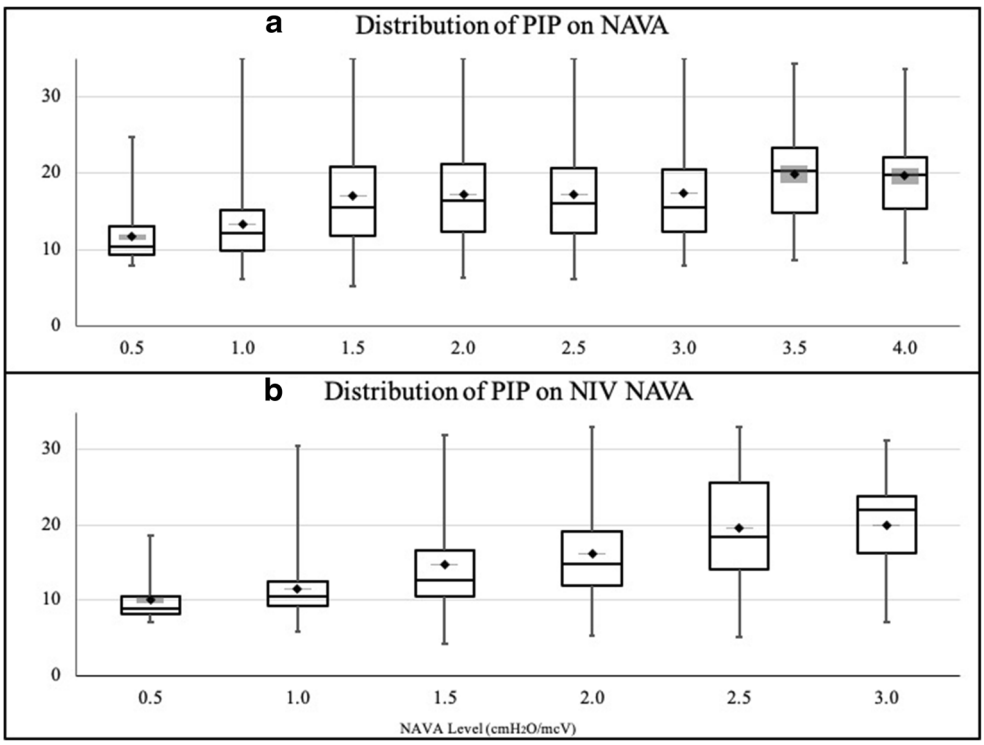

Fig. 4 Distribution of PIP by NAVA level for neonates on NAVA (panel **a**) and NIV NAVA (panel **b**). The black diamonds are mean values and the gray shaded lines are the confidence intervals. The box plots show the median and first and third quartiles. The whiskers are the minimum and maximum values. Visual examination of box plots indicates that the PIP rises at a faster rate as NAVA level increases in the NIV-NAVA group than it does in the NAVA group

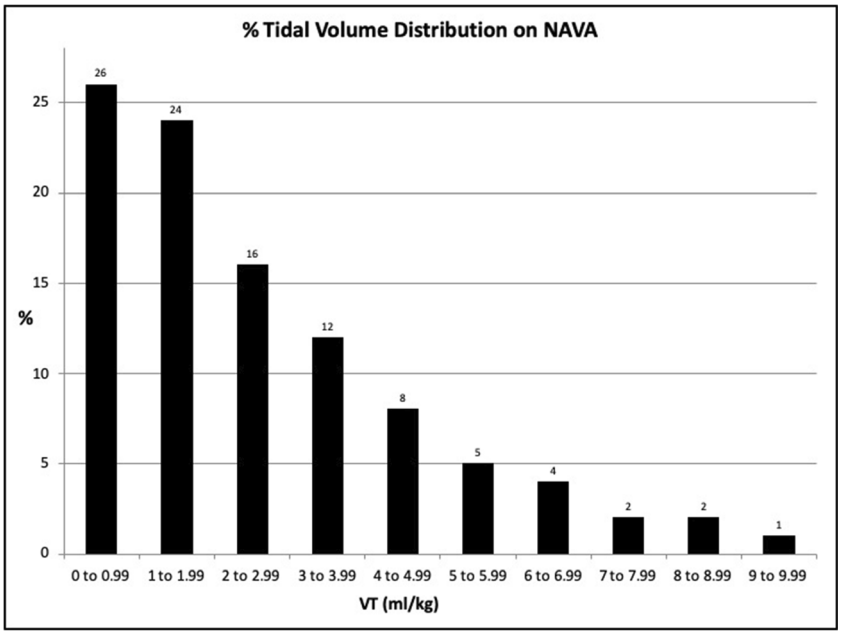

Fig. 5 Percent breath distribution for VT in 1-ml/kg increments on invasive NAVA

proportion (< 5%) were in the 30–35-cmH_2O range. The augmented PIPs likely represent lung recruitment breaths, an expected phenomenon commonly observed in premature neonates [21, 22]. The wide range of pressures generated as illustrated from the pressure distribution curve are consistent with neural respiratory pattern variability, an intrinsic property of breathing. Mechanical ventilation has been shown to negatively impact respiratory variability. Due to its unique neuro-respiratory coupling capability, NAVA ventilation has been found to superiorly support innate respiratory variability as opposed to other more monotonous modes of traditional ventilation [23].

Prevention of ventilator-induced lung injury remains a high priority and current evidence supports the use of VTV [2, 3, 24]. There are many different volume ventilation strategies, some which have a volume guarantee option, to assist the provider in achieving consistent tidal volumes [25, 26]. However, these strategies assume that tidal volume delivery should be relatively consistent for each breath. Neonates < 32 weeks gestation on continuous positive airway pressure were found to have an average VT of 4.4 ml/kg with a wide range of 2.6–7.2 ml/kg [27]. Typical VT ranges to initiate VTV range from 4 to 7 ml/kg [3, 4, 14] but in a survey from European neonatal intensive care units, 18% used VT > 7 ml/

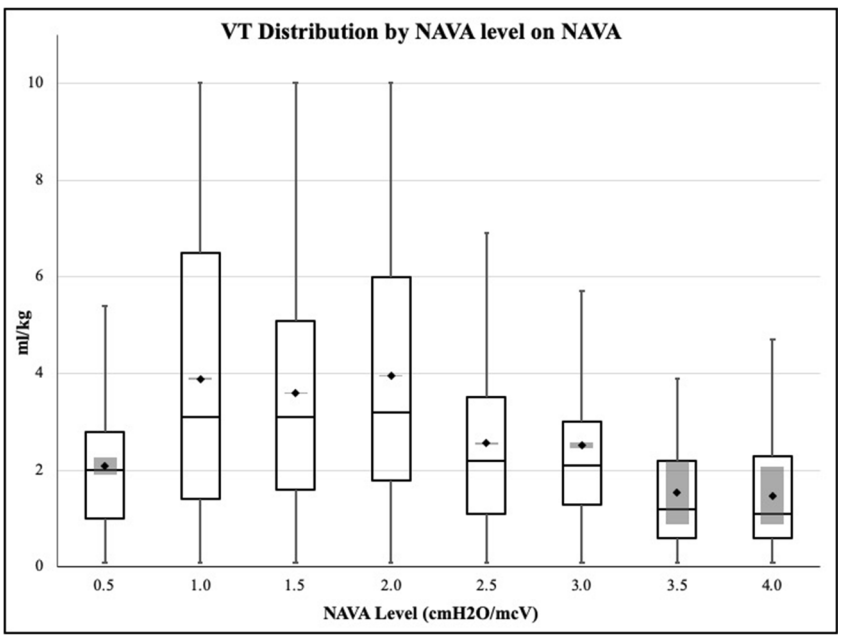

Fig. 6 Distribution of VT by NAVA level for neonates on NAVA. The black diamonds are mean values and the gray shaded lines are the confidence intervals. The box plots show the median and first and third quartiles. The whiskers are the minimum and maximum values

kg [4]. Although some authors have suggested that VT > 8 ml/kg can cause volutrauma [28, 29], it is important to note that any positive pressure ventilation can cause cyclic trauma up to 86,000 times/day [30]. It may be the repetitive shearing force caused by exposure to these high VTs that causes volutrauma and not the high VT itself. Alternatively, provision of inadequate tidal volumes can also increase the risk of lung injury. This finding was observed in a study which randomized premature neonates to receive either VTs of 3 ml/kg as compared to 5 ml/kg during the acute phase of respiratory distress syndrome [28]. The tracheal aspirates of the group receiving 3 ml/kg VT had significantly higher levels of pro-inflammatory markers. The ventilator mode used during this study was synchronized intermittent positive pressure ventilation that included a volume guarantee feature, with the ultimate goal of delivering consistent tidal volumes. The tidal volumes reported from our study averaged around 3 ml/kg with a wide range noted within a subject (Fig. 2). Tidal volume variation has been recognized as a normal finding in healthy subjects [23, 31]. In the adult population, decreased respiratory variability has been associated with increased mortality [32]. The neural breathing pattern in preterm neonates has been shown to be even more variable than in older children and adults. Breathing sighs are common in this population and may explain the intermittent high PIPs and VTs seen in this study [22]. By assisting with the plastoelastic stretching of lung tissue and respiratory muscles, sighs play an important role in improving lung compliance, reducing airway resistance, and optimizing lung volume recruitment [21, 33]. The high PIP and VTs observed in this study may be intermittent sigh or recruiting breaths enabling optimal lung recruitment and potentially resulting in the subsequent predominance of low PIP and VT. Both average and median VT were significantly less than the 5 ml/kg volume currently recommended for volume-targeted neonatal ventilation [34] and both average and median PIP were well below the currently recommended PIP [15]. However, it remains to be seen if these wide ranges seen with NAVA ventilation improve clinical outcome.

NAVA facilitates optimal synchronization between the patient and the ventilator. Patient-ventilator asynchrony has been associated with worse patient outcomes [35]. Improved patient-ventilator interaction has been demonstrated in adult, pediatric, and neonatal patients ventilated with NAVA [36–39]. Improved synchrony improves ventilatory efficiency and may contribute to the lower PIP and VT observed in this study. With optimal synchronization, reducing alveolar overdistension and respiratory muscle unloading can be achieved. Several studies have demonstrated decreasing oxygen requirements along with lower PIP for very low birth weight neonates on NAVA compared to other ventilator modes [11, 38, 40–42]. In a recent prospective observational study, preterm and term neonates placed on NAVA ventilation compared to SIMV with PS not only had improved patient-ventilator interaction, but a significant reduction in apneic events [42].

NAVA level was chosen by the bedside provider based on the clinical status of the neonate including work of breathing, and blood gases. The sicker the neonate (with worse lung compliance), the more support needed and the higher the NAVA level set. On the highest NAVA levels (3.5–4 cmH_2O/mcV), the neonates generated the highest PIPs but were only able to generate low VTs. This most likely reflected the disease state that resulted in poor lung compliance.

Concern has been raised about excessive variability in PIP and a higher proportion of excessive VT on higher NAVA levels and the ability of the neonate's neural feedback to regulate their breathing [43]. Data from the current study did not show excessive VTs at higher NAVA levels but rather lower VTs consistent with poor lung compliance. It is therefore likely that providing high NAVA levels to neonates who may not need it (as was done in the titration study [43]) can result in excessive variability in PIP and a higher proportion of excessive VT but, when used appropriately in neonates with severe lung disease, VT and pressures are acceptable, suggesting evidence of intact neural feedback pathways.

Potential limitations of our study include inherent inaccuracies that can be associated with calculating exhaled tidal volumes at the expiratory valve of the Servo-i ventilator [44]. A recent study demonstrated the benefits of the circuit compliance compensation, which were used in this study, helping to assure more reliable exhaled VT [45]. In-line proximal sensors can also be used to measure volume; however, they can negatively impact patient care by increasing the amount of dead space, which can be very significant for the smallest of neonates. Our study did not include the use of proximal flow sensors due to their limited use in both NICUs used in the study. While the proximal sensor may have refined the accuracy of each measured VT, the overall distribution should remain unchanged. The Servo-i does not record leakage in the invasive mode so it is possible that expiratory VT measurements could be underestimated and may explain the number of breaths observed with VT less than 2 ml/kg. Unfortunately, this measurement problem is a challenge inherent to any ventilator offering a VTV mode. This was a descriptive study only, with inherent limitations including not being able to make inferences with regard to specifics such as disease state, gestational age, or birth weight. Future studies would include evaluating PIP and VT ranges at various gestational ages, chronologic ages, and disease states.

Potential statistical limitations are that this was an exploratory study without an a priori sample size analysis, utilizing a convenience sample, and without a specific hypothesis or research question. Rather, the goal of this study was to quantify and characterize the PIP and VT levels in a specific cohort. Interpretation of statistically significant results may have limited clinical value due to the very large sample size, which

provided a high level of statistical power to detect a very small effect, specifically in the one-way ANOVA which indicated a significant difference in VT by NAVA level. Examination of statistical assumptions for all ANOVA (*F*-tests) revealed minor departures from normality of residuals; however, the *F*-tests are known to be robust to these departures in large samples. VT and PIP data points were treated as independent during analysis. Although trends could be appreciated from the reported data, the PIP and VT values could not be linked by observation.

Regardless of the potential inherent limitations previously discussed, current bedside clinical and ventilator management is driven from available VT and PIP data. Therefore, from a pragmatic standpoint, the PIP and VT values presented in this study would be of value when working at the bedside with the Servo-i.

Conclusion

This is the first study to demonstrate the wide range of VT and PIP observed for preterm neonates on NAVA. The majority of breaths were well below the 20 cmH_2O or the 5 ml/kg currently recommended in the neonatal literature. While the trend in neonatal ventilation is headed in the direction of a more volume-focused strategy, NAVA enables the patient to receive both the desired PIP and VT on a breath-to-breath basis. Mechanical ventilation strategies, like NAVA, which promote native respiratory reflexes, appear intuitively superior to that of traditional modes of ventilation that strive to deliver unwavering tidal breaths. Although neonates on NAVA took occasional large breaths, we speculate that eliminating these sigh breaths would be detrimental to the preservation of an open lung concept. Prospective randomized trials comparing the clinical benefits of NAVA to other ventilation modalities in preterm neonates are needed, with a specific goal of evaluating both short- and long-term outcomes.

Authors' contributions HS and KF contributed to the study design, data collection, analysis, and writing of the manuscript. AP and NM contributed to the statistical analysis of the collected data and writing of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest HS and KF are speakers for Getinge and Chiesi. AP and NM have no conflicts to disclose.

Ethical approval Approved by Promedica and Akron Children's Hospital IRBs.

Informed consent Not required—retrospective study.

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