



Ultrasonographic assessment of diaphragmatic function in preterm infants on non-invasive neurally adjusted ventilatory assist (NIV-NAVA) compared to nasal intermittent positive-pressure ventilation (NIPPV): a prospective observational study

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Abstract

NIV-NAVA mode for respiratory support in preterm infants is not well-studied. This study aimed to describe the diaphragmatic function, diaphragmatic excursion (DE), and thickness fraction (DTF), in preterm infants < 30 weeks' gestation supported by NIV-NAVA compared to NIPPV using bedside ultrasonography. In this consecutive prospective study, DE, diaphragmatic thickness at end of expiration (DT_{exp}), end of inspiration (DT_{ins}), and DTF were assessed using bedside ultrasound. Lung aeration evaluation using lung ultrasound score (LUS) was performed for the two groups. Diaphragmatic measurements and LUS were compared for the 2 groups (NIV-NAVA group versus NIPPV group). Statistical analyses were conducted using the SPSS software version 22. Out of 70 infants evaluated, 40 were enrolled. Twenty infants were on NIV-NAVA and 20 infants on NIPPV with a mean [SD] study age of 25.7 [0.9] weeks and 25.1 [1.4] weeks respectively ($p=0.15$). Baseline characteristics and respiratory parameters at the time of the scan showed no significant difference between groups. DE was significantly higher in NIV-NAVA with a mean SD of 4.7 (1.5) mm versus 3.5 (0.9) mm in NIPPV, $p=0.007$. Additionally, the mean (SD) of DTF for the NIV-NAVA group was 81.6 (30) % vs 78.2 (27) % for the NIPPV group [$p=0.71$]. Both groups showed relatively high LUS but no significant difference between groups [12.8 (2.6) vs 12.6 (2.6), $p=0.8$].

Conclusion: Preterm infants managed with NIV-NAVA showed significantly higher DE compared to those managed on NIPPV. This study raises the hypothesis that NIV-NAVA could potentially improve diaphragmatic function due to its synchronization with patients' own breathing. Longitudinal studies to assess diaphragmatic function over time are needed.

Trial registry: Clinicaltrials.gov (NCT05079412). Date of registration September 30, 2021.

What is Known:

- NIV-NAVA utilizes diaphragmatic electrical activity to provide synchronized breathing support.
- Evidence for the effect of NIV-NAVA on diaphragmatic thickness fraction (DTF) and excursion (DE) is limited.

What is New:

- Ultrasonographic assessment of diaphragmatic function (DTF and DE) is feasible.
- In preterm infants, DE was significantly higher in infants supported with NIV-NAVA compared to those supported with NIPPV.

Keywords Diaphragm thickness · Diaphragm excursion · Ultrasound · Preterm infant · Non-invasive neurally adjusted ventilatory assist

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Extended author information available on the last page of the article

Introduction

Over the past few decades, avoidance of invasive mechanical ventilation (IMV) and promoting of the use of non-invasive ventilation (NIV) in infants born prematurely has been accepted as a standard of care to reduce lung injury and subsequent development of bronchopulmonary dysplasia (BPD) [1]. Although nasal continuous positive airway pressure (nCPAP)

is the most frequently used NIV mode for infants born before 32 weeks gestation, NIPPV was found to decrease the incidence of reintubation within 2–7 days of life compared to nCPAP [2]. Furthermore, synchronized NIPPV is considered the most effective NIV in preventing extubation failure in preterm neonates with respiratory distress syndrome [3]. The advantages of NIPPV over nCPAP include the ability to deliver higher mean airway pressure (MAP) and carbon dioxide (CO₂) clearance [4, 5].

Recently, neurally adjusted ventilatory assist (NAVA) for invasive and non-invasive ventilation (NIV-NAVA) has emerged as a new respiratory support mode for preterm infants with respiratory insufficiency. Typically, NAVA mode (invasive and non-invasive) uses the electrical activity (Edi) of the diaphragm to trigger, set the amount of pressure, and cycle off the ventilator which in turn reduces asynchrony during NIV [6, 7]. In comparison to NIPPV, several studies have reported that NIV-NAVA is associated with a higher success rate of preventing reintubation [8–10], alongside fewer episodes of bradycardia and apnea of prematurity per day [11]. However, data regarding the effect of NIV-NAVA compared to NIPPV on diaphragmatic function and dimensions in preterm infants remains unknown.

Lung ultrasound (LU) has been increasingly used in neonates as a non-invasive and radiation-free imaging modality to assess lung aeration and diaphragm function. Moreover, there is a growing interest among researchers in using ultrasound to monitor the evolution of diaphragmatic contractility and dimensions during IMV, for clinical and research purposes [12–15]. Several parameters have been investigated to evaluate diaphragmatic functions, such as diaphragmatic excursion (DE) and diaphragmatic thickness and its fraction (DTF). While DE is known as the distance in which diaphragm can move during the respiratory cycle, DTF is a ratio between diaphragm thickness during inspiration and expiration [16, 17]. Although data about interpreting those parameters in preterm infants are still emerging, high DE was found to be a good indicator for prediction of extubation success in preterm infants < 32 weeks [18]. Likewise, DTF was found to be greater in preterm infants with BPD indicating increased diaphragmatic function to compensate for or the underlying parenchymal disease in this population [19]. Despite NIV-NAVA utilizes diaphragmatic electrical activity to provide synchronized breathing support, evidence for the effect of NAVA on DTF and DE is scarce.

We hypothesized that infants on NIV-NAVA will have better diaphragmatic function (DE and DTF) compared to infants on NIPPV. Thus, in this study, our primary objective was to characterize the DE, diaphragmatic thickness at end of expiration (DT_{exp}) and end of inspiration (DT_{ins}), and DTF in preterm infants (< 30 weeks' gestation) who were managed on NIV-NAVA compared to those managed on NIPPV using bedside ultrasonography. The secondary objective was

to evaluate lung aeration using lung ultrasound score (LUS) in infants on NIV-NAVA compared to those on NIPPV.

Methods

Study design

We conducted a consecutive prospective study between March 2020 and November 2021 on eligible infants who were admitted to the neonatal intensive care unit (NICU) at Mount Sinai Hospital, Toronto, Canada. Local research ethics approval was obtained (Mount Sinai Hospital REB (19–0324-E), and consecutive patients were enrolled after informed written consent was obtained from parents or guardians. This study was registered with the US Library of Medicine clinical trials registry, www.clinicaltrials.gov (NCT: 05,079,412). Registration has been delayed because of concomitant COVID pandemic announcement that led to withhold all interventional studies include this study for almost a year. Reporting of this study followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) Statement [20].

Study participants

Consecutive infants born at < 30 weeks' gestation who were receiving NIV-NAVA or NIPPV at 2–4 weeks after birth and for at least 24 h at the time of recruitment were included. Infants who had congenital or chromosomal abnormalities, neuromuscular disease, known lung malformation or diaphragm dysfunction, or whose parents declined to consent were excluded.

Respiratory management for preterm infants < 30 weeks gestational age

Respiratory management of preterm neonates < 30 weeks' gestation at our unit was by unit guidelines developed as part of "Bronchopulmonary Dysplasia Prevention bundle." The primary mode of non-invasive ventilatory support for infants born at < 24 weeks' gestation post-extubation is nasal intermittent positive pressure ventilation (NIPPV). Infants born at ≥ 24 weeks' gestation and spontaneously breathing are initiated on nCPAP (6–10 cmH₂O). If infants experience bradycardia and/or apnea while on nCPAP, they will be transitioned to NIPPV. FiO₂ is titrated to maintain SpO₂ within the target range (91–95%). Given the limited number of NAVA ventilators available in our unit during the study period, NIV-NAVA was used as a rescue NIV respiratory mode for cases failing NIPPV (FiO₂ > 0.4–0.5 to maintain oxygen saturation target, and pCO₂ > 65 mmHg with a pH < 7.20) to prevent reintubation. Another indication

for the use of NIV-NAVA was the presence of significant abdominal distension that can potentially lead to compromised ventilation.

Study procedure

All eligible infants were consecutively approached for the parent's consent. We evaluated diaphragmatic thickness (DT) and DE for all enrolled infants using bedside ultrasound (US). We used a high-resolution L20–5 MHz linear probe for the measurement of DT and a C10–3 MHz curvilinear probe for assessing DE (Z. One—Mindray, Inc.). All US assessments were undertaken using the standard technique while infants were in the supine position. Scans were performed either before or 1 h after feeding to avoid any concerns of a full stomach on diaphragmatic assessment. Infants were on continuous cardiorespiratory monitoring for apnea, bradycardia (heart rate < 80 beats per minute), and desaturation (oxygen saturation < 85%) events during the scan. Sonographic assessment of the diaphragm was completed by personnel trained in point-of-care neonatal US with a minimum of 6 months of experience in lung and diaphragm ultrasounds. To minimize errors in measurements and improve our measurement accuracy, we standardized the technique for obtaining diaphragmatic views and how to measure diaphragm thickness and excursion among all investigators prior to study enrollment.

Using a recently published standardized technique [12, 19, 21–25], the right hemidiaphragm was assessed with the infant in a relaxed state facilitated by modified swaddling and occasionally pacifier administered by a second

person. For DE measurements, the probe was placed sub-costal between the anterior axillary and midclavicular line with a curvilinear probe using a standardized protocol for image acquisition. DE was measured as the difference in the position of the outer line of the diaphragm in M-mode at peak inspiration and expiration (Fig. 1a). DT was measured at the zone of apposition where thickening and shortening of the diaphragm could be appropriately evaluated. DT was obtained by placing the linear transducer at the 9th or 10th intercostal space near the mid-axillary line while the transducer was perpendicular to the chest wall [23, 24]. By B-mode, the diaphragm was identified as the hypo-echoic area (muscular layer) bordered by two echogenic lines of the diaphragmatic pleura (upper line) and peritoneum (lower line). Using M-mode tracing, the end of expiratory and inspiratory DT was calculated by determining the maximum perpendicular distance between the pleural and peritoneal layers, measuring only the distance of the hypoechoic area (Fig. 1b). To assess the efficiency of the diaphragm as a pressure generator, the DTF was determined [25]. DTF was calculated as the change in DT_{exp} DT_{ins} using the following formula:

$$DTF = \frac{[(\text{inspiratory thickness} - \text{expiratory thickness})]}{\text{expiratory thickness}} \times 100$$

For each diaphragm parameter (DT_{exp} , DT_{ins} , DTF, and DE), the average from at least three respiratory cycles was reported to reduce the risk of over or underestimating the diaphragmatic measurements [26]. Standard neonatal LU views, three chest areas on each side (upper anterior, lower anterior and lateral) were obtained, and LUS using grading

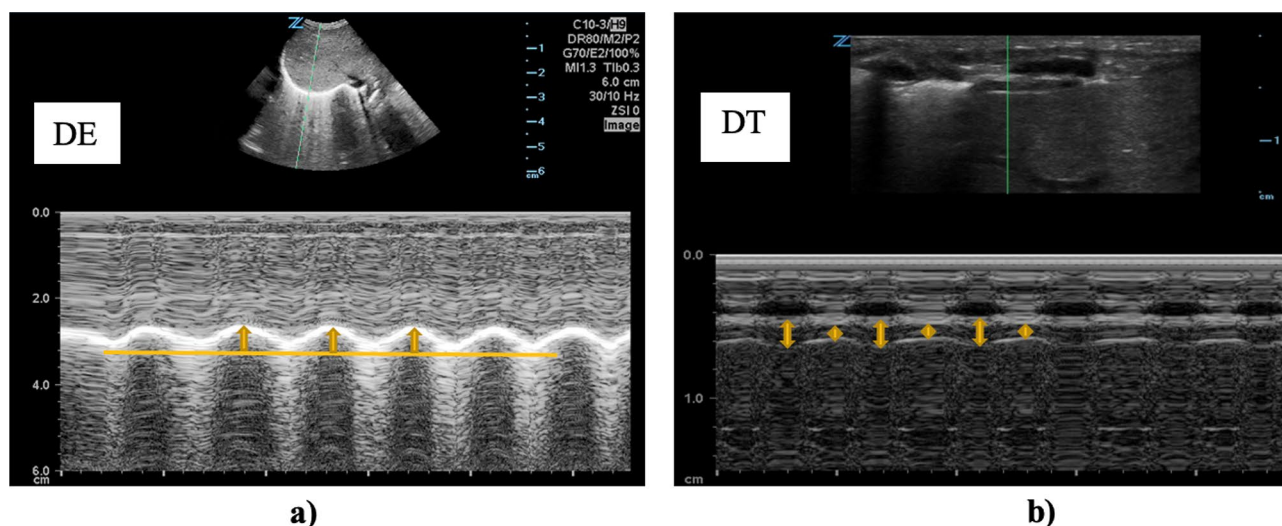


Fig. 1 **a, b** Measurement of diaphragmatic excursion and thickness. **a** Measurement of diaphragmatic excursion using M-mode from a study patient, marked by the length of the orange arrows pointing up. **b** Measurement of diaphragmatic thickness at the end of inspiration

and expiration using M-mode from a study patient, marked by the vertical distance (orange bidirectional arrows) between the 2 layers of diaphragm

score (ranges from 0–18 points) were determined as previously described [27, 28].

At the end of the study, all scans for the two groups were anonymized. All scans collected during the study were kept confidential and securely locked in computerized files saved on hospital drive which is password protected. Assessment of diaphragm function (DE and DTF) was performed by one of the investigators who was blind to study groups. Similarly, LUS was evaluated by another study investigator who was unaware of the study groups or results of diaphragmatic measurements of the study patients. To assess the inter-observer correlation, 25% of the anonymized study scans ($n = 10$ cases of DT and 10 cases of DE) were randomly assigned and reevaluated. Measurements were compared, and the intra-class correlation coefficient (ICC) was calculated.

Outcomes and clinical data

The primary outcome was the sonographic evaluation of DE, DT_{exp} , DT_{ins} , and DTF for infants born at < 30 weeks' gestation after receiving NIV-NAVA or NIPPV for ≥ 24 h. Secondary outcome was LUS for the two groups. Demographic and respiratory data at the time of the scan was collected. Typically, respiratory parameters are documented by respiratory therapist or bedside nurse every hour in the patient electronic medical record. The average from three consecutive measured PIP and MAP prior to LUS scan was reported to minimize risk of bias.

Sample size

A convenience sample was planned over one year (the study period) since no previous data on DE or DTF in preterm infants on NIV-NAVA was available. Due to COVID-19 pandemic, study recruitment was extended until November 2021.

Statistical analysis

Statistical analysis was performed using commercially available software (SPSS for Windows Inc. Version 22, Chicago, Illinois). The Kolmogorov–Smirnov test was performed to examine the distribution of data. Independent Student t test was used to compare continuous parametric variables to determine the differences between groups; Mann–Whitney U test was used for continuous non-parametric variables; chi-square test (χ^2) or Fisher exact test was used for categorical variables when appropriate. Clinical data and ultrasonography measurements were presented as mean and standard deviation or median and interquartile range for continuous variables or frequency and percentages for categorical variables. The ICC was determined for variables with continuous

measurements (mixed factorial design). We calculated the ICC using 30% of the images, which were evaluated by another individual blinded to the groups. p values less than 0.05 were considered significant.

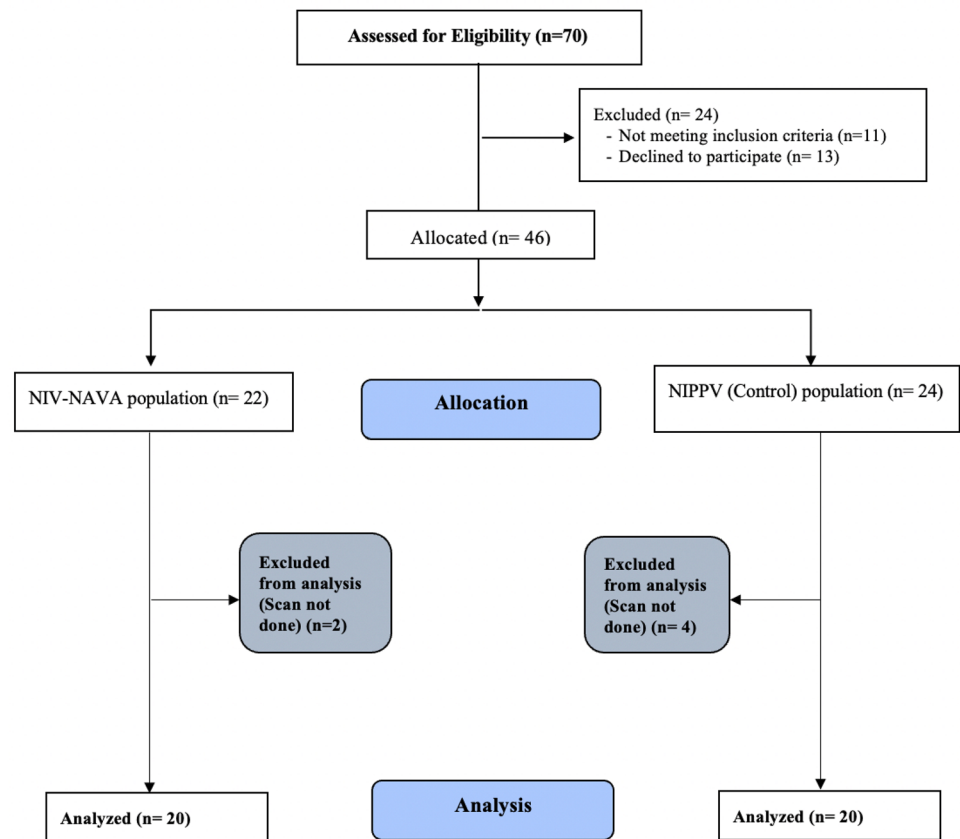
Results

We evaluated 70 infants born at < 30 weeks' gestation in a primary screen, of whom 46 cases met eligibility and consented to participate. Out of the 46 consented patients, 40 infants completed the study protocol (20 infants in each group). Six infants (4 cases in the NIPPV group and 2 infants from NIV-NAVA group) were not scanned due to timing issues and were excluded (Fig. 2). Baseline characteristics and respiratory status prior to the LU scanning of the two groups were summarized in Tables 1 and 2. There was no significant difference between the NIV-NAVA group compared to the NIPPV group regarding birth gestation (GA) or postmenstrual age (PMA) at the time of the scan. DE was significantly higher in NIV-NAVA [mean SD 4.7 (1.5)] versus [3.5 (0.9)] in NIPPV, $p = 0.007$ (Table 3). DTF was higher in NIV-NAVA compared to NIPPV group [mean (SD) 81.6 (30) vs 78.2 (27), $p = 0.71$]. There was no significant difference regarding DT_{exp} and DT_{ins} between groups. Both groups showed relatively high LUS but no significant difference [mean (SD) 12.8 (2.6) versus 12.6 (2.6) $p = 0.8$] (Fig. 3). Duration of IMV and incidence of BPD did not show significant difference between NIV-NAVA and NIPPV group [mean (SD) 5.35 (6.2) days versus 3.35 (4.4) days $p = 0.24$] and [80% versus 70% $p = 0.85$], respectively.

We found a strong inter-observer agreement for the measurement of DT and DE (ICC 0.86 [95% confidence interval (CI) 0.84–0.87] and 0.93 [95% CI 0.91–0.94] respectively). The ultrasonographic exams were generally well tolerated, and none of the scans were aborted because of bradycardia or desaturation during the ultrasonographic exams.

Discussion

Our study is the first to report that DE was significantly higher in preterm infants on NIV-NAVA compared to DE in infants supported by NIPPV. The significantly higher DE in preterm infants supported with NIV-NAVA can be explained by the fact that this mode of ventilation has a better patient-ventilator synchronization which will eventually augment diaphragmatic contractility. Several studies have suggested that better DE indicates improved diaphragmatic function and can potentially predict successful weaning from

Fig. 2 Study flow diagram

mechanical ventilation [29, 30]. Our results aligned with Hadda et al., who randomized adult patients to either invasive NAVA or conventional ventilators. Authors of this study

found that invasive NAVA was associated with a higher DE, in comparison to patients supported by conventional ventilators [31].

Table 1 Baseline characteristics of the study population

	NIPPV group (n = 20)	NIV-NAVA group (n = 20)	p value
Gestational age at birth (week), median (IQR)	25.9 (25.4–26.3)	24.6 (24–26.3)	0.24
Birth weight (gram), mean (SD)	756 (657–895)	700 (592–795)	0.37
Male sex, n (%)	13 (65%)	12 (60%)	0.74
Mode of delivery (caesarian), n (%)	11 (55%)	12 (60%)	0.75
APGAR score at 5 min, median (IQR)	8 (5–9)	7 (4–8.5)	0.35
Antenatal steroid, n (%)	17 (85%)	19 (95%)	0.29
Chorioamnionitis, n (%)	10 (50%)	13 (65%)	0.34
Surfactant n (%)	20 (100%)	19 (95%)	0.31
SNAP-II scores, median (IQR)	14 (5–19.7)	14 (5–14)	0.67
Sepsis prior to US scan, n (%)	3 (15%)	2 (10%)	0.63
HsPDA, n (%)	10 (50%)	9 (45%)	0.75
Duration of IMV before the scan (days), median (IQR)	2 (0–4.7)	3.5 (0–11)	0.43
BPD, n (%)	16 (80%)	14 (70%)	0.85
Corrected age (weeks) at US scan, median (IQR)	28.6 (27.1–29.3)	27.7 (16.5–29.9)	0.88
Weight (grams) at US scan, median (IQR)	880 (800–1045)	910 (767–1015)	0.78

Data expressed as median (IQR) or as number (%)

IQR interquartile range, NIPPV non-synchronized non-invasive positive pressure ventilation, NIV-NAVA non-invasive neurally adjusted ventilatory assist, SNAPE II Score for Neonatal Acute Physiology-Perinatal Extension

Table 2 Respiratory status prior to the US scan

	NIPPV group (<i>n</i> = 20)	NIV-NAVA group (<i>n</i> = 20)	<i>p</i> value
Postnatal systemic steroid, <i>n</i> (%)	0 (0%)	2 (10%)	0.11
Respiratory parameters at the scan			
PIP median (IQR)	16 (15.3–18)	15.5 (13–18)	0.41
PEEP median (IQR)	8 (7–10)	9 (7–10)	0.15
MAP median (IQR)	10.5 (10–12)	12 (8.8–15.3)	0.23
FiO ₂ median (IQR)	28.5 (22.3–33.8)	27 (23–35.5)	0.82
NAVA level median (IQR)	NA	1.7 (1.2–2)	NA
Edi peak median (IQR)	NA	5.3 (4.2–7.7)	NA
Edi min median (IQR)	NA	2.5 (1.03–3.9)	NA
RR (breath/min) median (IQR)	37 (28.8–50)	45 (38.3–57.5)	0.13
pH median (IQR)	7.35 (7.25–7.43)	7.25 (7.23–7.33)	0.26
pCO ₂ median (IQR)	58 (40.3–67.5)	53 (50–67.5)	0.71
RSS (resp severity score) median (IQR)	2.7 (2.2–4.2)	3.3 (2.1–5.6)	0.49
Duration of NIV-NAVA prior to the scan (Days) median (IQR)	NA	1 (1–2.8)	NA
Duration of NIPPV prior to the scan (Days) median (IQR)	10 (5.3–11)	9.5 (5.3–15)	0.74
Total duration of NIV before the scan (Days) median (IQR)	12.5 (10–17)	12 (8–26.3)	0.86

Data expressed as median (IQR) or as number (%)

IQR interquartile range, *NIPPV* non-synchronized non-invasive positive pressive ventilation, *NIV-NAVA* non-invasive neurally adjusted ventilatory assist, *RR* respiratory rate, *RSS* respiratory severity score

Alam et al. [32] reported that successful extubation was significantly correlated with DE with an area under the curve (AUC) of 0.83 ($p < 0.001$) and sensitivity 77.8% and specificity 84.6%. These results were consistent with several other studies that showed promising findings for using NIV-NAVA to facilitate extubation in preterm infants [10, 33, 34]. During our study period, NIV-NAVA was used as rescue mode for infants who failed NIPPV. Currently, attending physicians in our unit are recommending the use of NIV-NAVA as the primary NIV mode post extubation to improve rate of successful extubation. Interestingly, NAVA has been useful in preterm neonate with postsurgical unilateral diaphragmatic paralysis and cases of congenital diaphragmatic hernia with encouraging results [35–37].

Furthermore, Rehan et al. found that a higher level of PEEP in preterm infants supported by nCPAP causes significant reduction in DE suggesting impaired diaphragmatic functions with high PEEP [38]. While the PEEP used in

NIV-NAVA and NIPPV in our study were relatively high in both groups, infants on NIV-NAVA had less reduced DE compared to DE in infants receiving similar PEEP on NIPPV.

Additionally, our study did not show a significant difference between the 2 groups regarding the diaphragmatic thickness (DT_{ins} and DT_{exp}) or DTF. There is no available data regarding the effect of NIV-NAVA on diaphragmatic dimensions in preterm infants to compare with our findings. However, in a recent study conducted in our unit by Yeung et al., authors reported higher DTF in preterm infants who were diagnosed with BPD [19]. Despite up to 80% of our study population had been diagnosed with BPD at 36 weeks PMA, our results did not show similar results as Yeung et al. This could be explained by the fact that our study was done during the earlier neonatal period before BPD established. Another potential reason of not finding difference in DTF between groups was due to the small sample size of our study. In contrast, our results were

Table 3 Diaphragmatic measurements and lung ultrasound score

	NIPPV group (<i>n</i> = 20)	NIV-NAVA group (<i>n</i> = 20)	<i>p</i> value
Diaphragmatic excursion (mm), mean (SD)	3.5 ± 0.9	4.7 ± 1.5	0.007
Inspiratory diaphragm thickness (mm), mean (SD)	1.18 ± 0.4	1.18 ± 0.3	0.99
Expiratory diaphragm thickness (mm), mean (SD)	0.69 ± 0.3	0.67 ± 0.2	0.78
Diaphragmatic thickness fraction (mm), mean (SD)	78.2 ± 27	81.6 ± 30	0.71
Lung ultrasound score, median (IQR)	12.6 ± 2.6	12.8 ± 2.6	0.81

Data expressed as mean (SD; standard deviation) or as median (IQR)

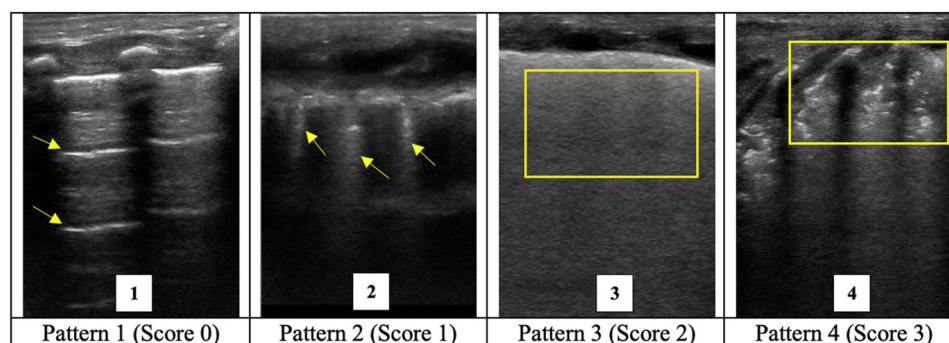


Fig. 3 Lung ultrasound patterns and scoring: Lung ultrasound findings were categorized into 4 patterns **1** A-lines pattern (score=0) indicates presence of A-lines artifact, pleural line sliding, and less than 3 B-lines; **2** Nonconfluent B-lines pattern (interstitial syndrome, score=1), indicates more than 3 B-lines, and pleural line sliding;

3 Confluent B-lines pattern (white lung pattern, score=2) indicates confluent B-lines, and pleural line sliding; **4** consolidation pattern (subpleural consolidation > 5 mm, score=3) with absent A-lines, confluent B lines

aligned with Hadda et al., who evaluated the DTF in adults' patients admitted to ICU with acute respiratory failure, to evaluate the effect of invasive NAVA on the diaphragmatic function. In this study, investigators found no significant difference in DT and DTF between invasive NAVA and conventional ventilator [31].

Furthermore, we evaluated lung aeration using LUS in both groups. Although we found no significant difference between NIV-NAVA and NIPPV regarding the LUS, we noted that LUS were significantly high in both groups when compared with our cut-off score (> 10 points) for early prediction of BPD in similar preterm population [27]. The high LUS in both groups is likely because our study population were born at a mean GA of 25 weeks' gestation with very immature lung. Several studies that evaluated lung aeration using LUS in the first 2 weeks of postnatal age in preterm infants found similar high LUS that accurately predict the diagnosis of BPD at 36 weeks PMA [39–41].

We acknowledge our study limitations. First, we had a small sample size that could be attributed to interrupted/low recruitment rate due to the COVID-19 pandemic. Second, the study design was based on consecutive recruitment of all eligible patients but lacked randomization. Thirdly, we did not do a serial ultrasonographic assessment to evaluate the changes of diaphragmatic dimensions and functions over time while infants were supported by these two types of NIV. Another limitation is that infants in the NIV-NAVA group were scanned after short duration post transitioning from NIPPV and the risk of “carryover effect” cannot be ruled out completely. Finally, diaphragm ultrasound is operator dependent; therefore, some variations in the measurements are not uncommon. However, our study results have shown high interobserver reliability which validate, to some degree, the study findings.

Conclusion

In infants born at < 30 weeks' gestation, NIV-NAVA was associated with significantly higher DE compared to NIPPV reflecting improvement in the diaphragmatic functions. There were no significant differences regarding other measurement such as DT_{exp} , DT_{ins} , DTF, and LUS. Further studies, with a larger sample size and serial assessment of the diaphragm are needed to draw a firm conclusion.

Abbreviations DE: Diaphragm excursion; DT_{exp} : Diaphragm thickness at end of expiration; DTF: Diaphragm thickness fraction; DT_{ins} : Diaphragm thickness at end of inspiration; ICC: Intraclass correlation coefficient; IMV: Invasive mechanical ventilation; LU: Lung ultrasound; LUS: Lung ultrasound score; NAVA: Neurally adjusted ventilatory assist; nCPAP: Nasal continuous positive airway pressure; NICU: Neonatal intensive care unit; NIPPV: Nasal intermittent positive pressure ventilation; NIV: Non-invasive ventilation; RCT: Randomized control trial; SD: Standard deviation

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Guarantor AM, who takes responsibility for the content of the manuscript, including the data and analysis (Original Research).

Authors' contributions ME and LT has equal contribution to the study design, data collection, and manuscript writing. AM had full access to all of the data and takes responsibility for the content of this manuscript, including study design, data, and data analysis. The study design was conducted by LT, ME, JI, NN, and AM; data collection was performed by JI, ME, and AM. Data analysis was performed by NN and AM. The manuscript was prepared by ME and LT then edited by JI, NN, and AM. All authors of this study approved the final draft of the manuscript.

Data availability All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declarations

Ethics approval Local research ethics approval was obtained (Mount Sinai Hospital REB (19–0324-E), Toronto, ON, Canada).

Consent to participate Written informed consent was obtained from parents or guardians.

Consent for publication All the authors have seen the final version of the manuscript and gave their full consent for the publication.

Conflicts of interest The authors declare no competing interests.

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