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ORIGINAL ARTICLE

Non-invasive neurally adjusted ventilatory assist in preterm infants with RDS: effect of changing NAVA levels

Julie Lefevere[1,4] · Brenda Van Delft[1] · Michel Vervoort[2] · Wilfried Cools[3] · Filip Cools[1]

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Abstract

We aimed to examine the effect of changing levels of support (NAVA level) during non-invasive neurally adjusted ventilatory assist (NIV-NAVA) in preterm infants with respiratory distress syndrome (RDS) on electrical diaphragm activity. This is a prospective, single-centre, interventional, exploratory study in a convenience sample. Clinically stable preterm infants supported with NIV-NAVA for RDS were eligible. Patients were recruited in the first 24 h after the start of NIV-NAVA. Following a predefined titration protocol, NAVA levels were progressively increased starting from a level of 0.5 $cmH_2O/\mu V$ and with increments of 0.5 $cmH_2O/\mu V$ every 3 min, up to a maximum level of 4.0 $cmH_2O/\mu V$. We measured the evolution of peak inspiratory pressure and the electrical signal of the diaphragm (Edi) during NAVA level titration. Twelve infants with a mean (SD) gestational age at birth of 30.6 (3.5) weeks and birth weight of 1454 (667) g were enrolled. For all patients a breakpoint could be identified during the titration study. The breakpoint was on average (SD) at a level of 2.33 (0.58) $cmH_2O/\mu V$. With increasing NAVA levels, the respiratory rate decreased significantly. No severe complications occurred.

Conclusions: Preterm neonates with RDS supported with NIV-NAVA display a biphasic response to changing NAVA levels with an identifiable breakpoint. This breakpoint was at a higher NAVA level than commonly used in this clinical situation. Immature neural feedback mechanisms warrant careful monitoring of preterm infants when supported with NIV-NAVA.

Trial registration: clinicaltrials.gov NCT03780842. Date of registration December 12, 2018.

What is Known:
- *Non-invasive neurally adjusted ventilatory assist (NIV-NAVA) is a safe, feasible and effective way to support respiration in preterm infants.*
- *Intact neural feedback mechanisms are needed to protect the lung from overdistension in neurally adjusted ventilatory assist.*

What is New:
- *Preterm infants with acute RDS have a similar pattern of respiratory unloading as previously described.*
- *Neural feedback mechanisms seem to be immature with the risk of insufficient support and lung injury due to overdistension of the lung.*

Keywords Interactive ventilatory support · Diaphragm · Infant · Premature · Respiratory distress syndrome · Newborn · Intensive care units · Neonatal · Respiration · Artificial

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✉ Julie Lefevere
Julie.lefevere@uzbrussel.be

[1] Neonatology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

[2] Department of Biotechnology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

[3] Interfaculty Centre Data Processing and Statistics, Vrije Universiteit Brussel (VUB), Brussels, Belgium

[4] Neonatology, (UZ Brussel), Laarbeeklaan 101, 1090 Jette, Belgium

Abbreviations

BW	Birth weight
CPAP	Continuous positive airway pressure
Edi	Electrical signal of the diaphragm
FiO_2	Fraction of inspired oxygen
GA	Gestational age
HR	Heart rate
NAVA	Neurally adjusted ventilatory assist
NIV-NAVA	Non-invasive neurally adjusted ventilatory assist
pCO2	Partial carbon dioxide pressure
PIP	Peak inspiratory pressure
RDS	Respiratory distress syndrome

RR	Respiratory rate
SD	Standard deviation
SpO_2	Oxygen saturation

Introduction

Neurally adjusted ventilatory assist (NAVA) is a diaphragm-triggered ventilation that uses the electrical signal from the diaphragm (Edi) to proportionally assist the patient's respiration. When there is no Edi-signal for a predetermined time (=apnea time), a back-up ventilation is provided. NAVA can be used as an invasive (via an endotracheal tube) or a non-invasive (via a nasal mask or nasal prongs: NIV-NAVA) ventilation mode [1]. Several clinical studies have shown that NAVA and NIV-NAVA are feasible, safe and effective in preterm neonates [2–6]. The NAVA level is the factor that converts the Edi signal in a proportional pressure. As the NAVA level increases, the workload is shifted from the patient to the ventilator. This allows the work of breathing to be unloaded from the patient to the ventilator. The breakpoint is the point at which the NAVA support is at a level where the patient's diaphragm is adequately unloaded. In order to locate this breakpoint for a specific patient, the NAVA level has to be increased progressively. With a given Edi, increasing NAVA levels will result in increasing Peak inspiratory pressures (PIP). Once the breakpoint is reached, the respiratory muscle unloading is sufficient and further increase in NAVA level will not result in a higher PIP, because there will be a suppression of the patient's inspiratory drive and the Edi will decrease [7].

Firestone et al. were the first to demonstrate that this neural feedback mechanism is intact in preterm infants ventilated with NAVA or NIV-NAVA [8]. A later study showed that the breakpoint changes before and after extubation from NAVA to NIV-NAVA [9]. In the study by Nam et al., these findings were not confirmed in preterm patients on invasive NAVA [10]. All these studies included preterm infants with various diseases and various postnatal ages. Data on preterm infants in the acute phase of respiratory distress syndrome (RDS) are lacking. These infants could eventually benefit a lot from optimal respiratory support in order to prevent intubation and mechanical ventilation.

In our neonatal unit the current approach for patients on NIV-NAVA is to start with a NAVA level between 1 and 2 $cmH_2O/\mu V$ and then titrating the NAVA level up or down depending on the Edi peak levels, partial carbon dioxide pressure (pCO_2) and signs of respiratory distress. Target Edi peak levels are between 10 and 15 µV. NAVA levels beyond 2 $cmH_2O/\mu V$ are rarely used.

The primary objective of this study was to investigate if a breakpoint could be determined in preterm infants in the early phase of acute RDS on NIV-NAVA. This could help us to define the ideal and individual starting settings for NAVA in these infants.

Materials and methods

Study design

A single-centre prospective exploratory study in a convenience sample was conducted in the neonatal intensive care unit at the Universitair Ziekenhuis Brussel from December 2018 to January 2021. The study serves as a pilot trial for a larger trial on NIV-NAVA and diaphragmatic activity in preterm infants in the future. Infants were eligible if they were born before 37 weeks' gestation and were supported with NIV-NAVA for RDS. They were included within 24 h after starting NIV-NAVA if they were clinically stable. In our unit, very preterm infants with RDS are primary treated with NIV-NAVA or with nasal CPAP. Current international guidelines only recommend nasal CPAP as primary non-invasive respiratory support for RDS, although there is some evidence that suggests that early non-invasive positive pressure ventilation (NIPPV) might be superior to nasal CPAP in decreasing respiratory failure and the need for intubation [11, 12]. Exclusion criteria included congenital malformations or abnormalities of the diaphragm or other parts of the respiratory system, more than 20% of time spent in back-up ventilation and hemodynamic instability or rapid respiratory deterioration on NIV-NAVA. The decision for NIV-NAVA as mode for respiratory support was made by the attending physician. NIV-NAVA was used as primary respiratory support, after CPAP-failure or as post-extubation support. All patients were ventilated with a Servo-n ventilator (Getinge, Sweden, System version 2.01). For all infants we used the Flexitrunk™ nasal interface (Fisher and Paykel®) with binasal prongs or nasal mask from varying sizes depending on the size of the nose and the nostrils according to the guide from the manufacturer. The hospital's medical ethics committee approved the study and signed written consent by the parents was obtained prior to inclusion in the study. The study was prospectively registered on clinicaltrials.gov (NCT03780842).

Outcomes

The primary objective was to evaluate the evolution in PIP and Edi with changing NAVA levels. Secondary outcomes included the effect on respiratory rate (RR), heart rate (HR), oxygen saturation (SpO_2), and fraction of inspired oxygen (FiO_2).

Procedure

Before starting the titration procedure, the ventilator limit for peak inspiratory pressure (PIP) was set to 35 cmH_2O (the maximum pressure that can be delivered to the patient is cut off at 30 cmH_2O). Infant demographics and baseline ventilator settings were recorded.

As a starting point, the NAVA level was reduced to 0.5 $cmH_2O/\mu V$ for 3 min. Next, the level was increased with 0.5 $cmH_2O/\mu V$ every 3 min until a maximum NAVA level of 4.0 cmH_2O /μV was reached. All other settings except for FiO_2 were kept constant throughout the study. FiO_2 was titrated to keep SpO_2 between 90 and 95%. A previous study performed in neonates using a similar titration protocol showed that a 3-min period was long enough to see a response in PIP and Edi [8].

HR and SpO_2 were recorded from the bedside monitor every 30 s. Data regarding the ventilation parameters were downloaded from the ventilator with SERVO tracker software (Getinge) and exported in an Excel file. These data include PIP, Edi peak and min, RR, FiO_2, NAVA level, leakage percentage and were recorded every second for the duration of the titration procedure (24 min). After the titration was completed, the level was returned to the initial NAVA level. The Edi-change or delta Edi (Edi peak – Edi min) was used for all analyses and will referred to in what follows as Edi. The average over each 3-min interval was used for all variables.

Statistical analysis

A convenience sample of 10 infants was prefigured in accordance with other studies on this topic [8–10]. PIP, delta Edi and NAVA level were plotted on a curve with PIP and Edi on the *Y*-axis and NAVA level on the *X*-axis. Visual inspection of the curve, as previously validated, by two independent examiners was used to determine the inflection point for PIP; this was called the breakpoint [8, 9, 13]. In addition, we conducted a patient-specific breakpoint analysis on the evolution of level specific averages with the segmented package in R. In case there was a difference between the visual inspection and the statistical analysis, we reviewed the PIP and Edi curves to see if we could visually agree with the statistical analysis.

Data were then combined by aligning each variable for the breakpoint and averaging the variables for each NAVA step above and below the breakpoint. PIP and Edi values were compared for each level positioned relatively compared to the assigned breakpoint, ranging from −2 to 2. To make the analysis, a linear mixed model was used to compare PIP and Edi between consecutive levels. A paired *t*-test was used to compare baseline NAVA level with the NAVA level at the breakpoint.

Linear mixed models were used to explain the evolution of the patients' data of RR, HR, and SpO_2 over consecutive NAVA levels, allowing for different trends before and after the breakpoint.

Results

Fourteen patients were recruited and underwent the titration protocol, due to technical defects data from two patients could not be analysed. Data from twelve infants were studied; they had a mean (SD) gestational age (GA) at birth of 30.6 (3.5) weeks (range 25 4/7 to 35 2/7 weeks), birth weight (BW) of 1454 (667) g (range 580 to 2570 g) and age at the time of the study of 1.3 (0.6) days (range 1 to 3 days). Five infants were on NIV-NAVA as primary respiratory support (all less than 30 weeks gestational age), five because of CPAP failure (all 32 weeks gestational age or more), and two as post-extubation respiratory support. Nine patients received surfactant therapy prior to inclusion in the study because of RDS with an oxygen requirement of more than 30% FiO_2. Baseline characteristics and ventilator settings of enrolled infants are detailed in Table 1. Individual patient characteristics are listed in Table 2 (Online Resource 1).

In all of our patients, we found the typical response when increasing the NAVA level. As the NAVA level is increased, PIP increases accordingly. At a specific NAVA level, further increases are no longer associated with increases in PIP, and Edi values start to decrease. The point at which this happens is called the breakpoint and could be identified in all patients. All PIP and Edi curves are presented as supplementary information in Online Resource 2. In four patients, the first visual inspection gave a different breakpoint than the statistical analysis (Online Resource 3). Nevertheless, in these cases, after thorough revision of the curves by two observers, there was decided to agree with the statistical breakpoint. All further analyses are done with the breakpoint defined by the statistical analysis. In some patients, a second rise in PIP was noticed after the plateau phase had been reached. The rise in Edi that is normally expected to be found in the lower range of NAVA levels was absent or minimal in most of the patients, and there was no clear relation with gestational age.

Figure 1 and Table 2 show the composite data of PIP and Edi for all patients, the breakpoint for the whole study group was at a mean (SD) NAVA level of 1.96 (0.66) $cmH_2O/\mu V$ (range 1 to 3.5 $cmH_2O/\mu V$). The mean (SD) plateau PIP at the breakpoint was 14.4 (2.8) cmH_2O. The range of overall observed PIP values was 5–32 cmH_2O. Changes in PIP between two consecutive levels below the breakpoint were only significant between level BrP – 0.5 and the breakpoint. As expected, PIP did not change significantly after the breakpoint. The combined Edi data showed no significant changes for consecutive NAVA levels. The NAVA level at the breakpoint was on average 0.66 $cmH_2O/\mu V$ (CI 0.16–1.16, $p = 0.01$) higher than the baseline NAVA level.

Mean (SD) RR was 65.0 (4.2) per minute, reflecting mild tachypnoea compatible with a population of preterm infants with RDS. A significant decrease of RR with increasing NAVA levels ($p < 0.0001$) was seen. On average, the RR decreased with 9.6 breaths per minute over the entire titration protocol. No clinically relevant relation between RR and the breakpoint was identified. Further inspection of the individual curves highlighted a strong variability in RR

Table 1 Infant characteristics and baseline settings

Characteristics	$N=12$
Gestational age at birth, mean weeks (SD, range)	30.6 (3.5, 25 4/7 – 35 2/7)
24–27 6/7 weeks, *n*	3
28–31 6/7 weeks, *n*	4
32–36 6/7 weeks, *n*	5
Birth weight, mean grams (SD, range)	1454 (667, 580–2570)
Male/female, *n*/*n*	6/6
Cesarean delivery, *n* (%)	10 (83)
Prenatal steroids (completed course), *n* (%)	8 (67)
Apgar score at 5 min, mean (SD)	8 (1.8)
CRIB II score (for infants ≤ 32 weeks)	6.7 (3.5)
Chorioamnionitis, *n* (%)	0 (0)
Age at the time of the study, mean days (SD, range)	1.3 (0.6, 1–3)
Surfactant therapy, *n* (%)	9 (75)
Caffeine, *n* (%)	8 (75)
Baseline NAVA settings, mean (SD)	
NAVA level ($cmH_2O/\mu V$)	1.3 (0.3)
PEEP (cmH_2O)	6.2 (0.4)
FiO_2 (%)	24 (5)
Apnea time (s)	3.5 (0.9)

per patient during the study, as typical for preterm infants. There were no significant changes in HR, SpO_2 and FiO_2 during the study. HR was always within normal range (100 to 180 bpm) and on average (SD) 139 (8.3) beats per minute, no bradycardic events occurred. SpO_2 was on average (SD) 95.6 (3.3) %. In two patients, mild desaturation occurred with a minimal oxygen saturation of 86% for less than 30 s. For most patients FiO_2 was stable during the protocol with an average (SD) FiO_2 of 24.1 (5.8) %. In one patient (GA 35 weeks, BW 2240 g), with severe RDS, a temporary rise in FiO_2 from 38 to 55% was needed to keep the oxygen saturation within the target range, this was seen at levels 2 and 2.5 $cmH_2O/\mu V$. No severe complications occurred.

Discussion

This is the first study exploring the effect of increasing NAVA levels in premature neonates in the early phase of RDS supported with NIV-NAVA. In all patients, a breakpoint could be identified, which is in line with previous reports in premature neonates at an older age and with other conditions [8, 9]. This study shows that also in the acute phase of RDS, premature neonates demonstrate a two-phased response to increasing NAVA levels. However, for all patients the decrease in Edi in NAVA levels beyond the breakpoint was very subtle or absent. In the combined data analysis there was no significant change in Edi in the NAVA levels beyond the breakpoint. The neural respiratory drive remains high even with NAVA levels beyond the breakpoint. This could be due to the relative inefficacy of non-invasive ventilation in premature neonates with large air leaks at the nasal interface or to the immaturity of the respiratory drive. This was also seen in a previous titration study where neonates were studied before and after extubation [9]. In some infants, a secondary rise in PIP in the higher range of NAVA levels was observed, suggesting that neural feedback mechanisms are insufficient or too immature to sufficiently suppress diaphragmatic activity at these high NAVA levels. On average, the maximum PIP was 15.2 cmH_2O, but intermittently higher PIP are possible because of the preterm neural breathing pattern with intermittent sigh breaths [14]. As only infants on non-invasive ventilation with large air leaks were studied, expiratory volumes could not be measured, and therefore, it remains unclear whether these higher PIPs are associated with important changes in tidal volume or minute ventilation. Nevertheless, this observation suggests that in this population of premature neonates, the protection mechanisms for overdistension of the lung are only functional until a certain level. Beyond a specific critical point, these mechanisms seem to fail, putting the lung at risk for overdistension. The physiological pathways responsible for this protection are still unknown. The Hering–Breuer reflex could explain this, although not confirmed in neonates [7, 8, 15]. A recent study of preterm infants on invasive NAVA also demonstrated that neural feedback mechanisms are insufficient in preterm infants [10].

With NAVA levels below the breakpoint, a concurrent rise in Edi, reflecting increased respiratory effort, is expected to be observed in order to maintain adequate minute ventilation. This rise in Edi at low NAVA levels was absent in

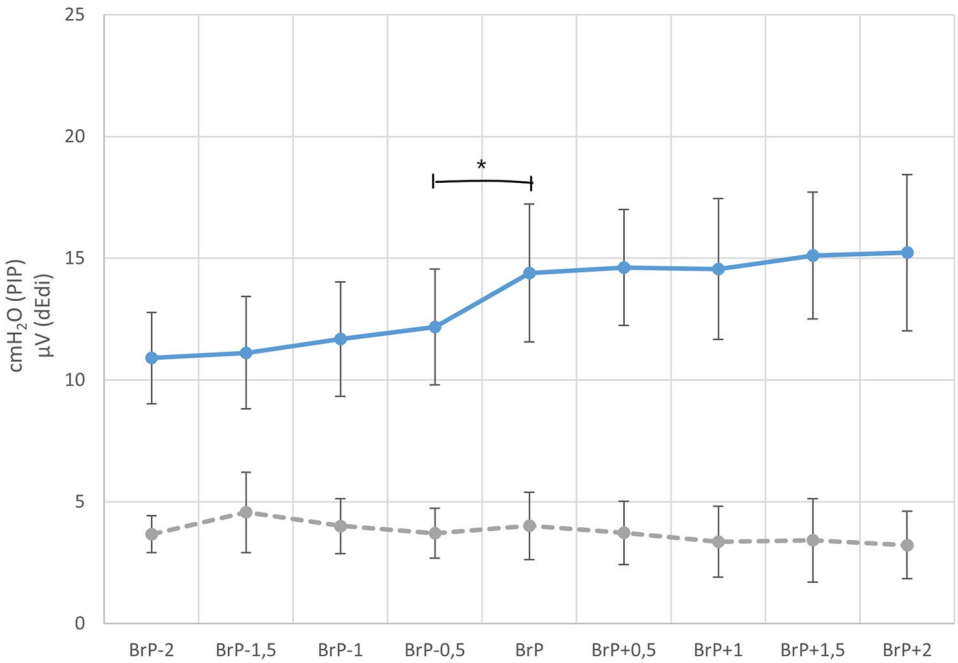

Fig. 1 Combined data of effect of changes in neurally adjusted ventilatory assist levels on peak inspiratory pressure (PIP in cmH_2O, solid line) and change in electrical activity of the diaphragm (dEdi in µV, dashed line) for all patients on non-invasive neurally adjusted ventilatory assist. Values are given as average values with standard deviation At NAVA levels below the breakpoint (BrP-2 to BrP-0.5) PIP increases with increasing NAVA level. After the breakpoint (BrP) is reached, there is no further increase in PIP with increases in NAVA level (BrP+0.5 to BrP+1). With even higher NAVA levels (BrP+1.5 and BrP+2) a small secondary rise in PIP is noticed. At NAVA levels below the breakpoint the dEdi remained constant, then decreased slightly as the NAVA level was increased beyond the breakpoint. At the highest NAVA levels (BrP+1.5 and BrP+2) no further decrease in dEdi was seen. *$p < 0.05$ between a 0.5 cmH_2O/µV change in the NAVA levels

several patients, and this was associated with an important fall in PIP in these infants. The combined data also showed no Edi rise in the NAVA levels below the breakpoint.

In general low NAVA levels were well tolerated for these short time periods of 3 min. This lack of compensation could also reflect an immaturity of the neural respiratory drive. Another possible explanation is that the duration of the interval between changes in NAVA level was too short to induce an adequate increase in respiratory drive. In a similar study by Nam et al., where longer intervals of 10 min were used, a significant rise in Edi in the lower NAVA levels was detected in patients on invasive NAVA [10].

Table 2 Combined data of effect of changes in neurally adjusted ventilatory assist levels on PIP and Edi

NAVA level	PIP (cmH_2O)	Edi (µV)
BrP-2	10.9 (1.9) (9.4–14.1)	3.7 (0.8) (2.4–4.4)
BrP-1.5	11.1 (2.3) (7.6–15.9)	4.6 (1.6) (2.5–8.5)
BrP-1	11.7 (2.3) (8.8–17.1)	4.0 (1.1) (2.3–5.6)
BrP-0.5	12.2 (2.4) (8.1–17.3)	3.7 (1.0) (2.2–5.6)
BrP	14.4 (2.8) (10.1–19.1)	4.0 (1.4) (2.1–6.6)
BrP+0.5	14.6 (2.4) (11.0–18.1)	3.7 (1.3) (2.1–6.7)
BrP+1	14.6 (2.9) (9.7–18.3)	3.4 (1.5) (1.6–6.4)
BrP+1.5	15.1 (2.6) (11.3–19.0)	3.4 (1.7) (2.0–7.2)
BrP+2	15.2 (3.2) (10.5–19.4)	3.2 (1.4) (2.2–6.4)

Data are represented as mean (SD) and range for each NAVA level below, at and beyond the breakpoint (BrP)

The breakpoint in our study patients seemed to be at slightly higher levels than the levels that are commonly used to support similar patients in our unit. Prior to enrolment, patients on NIV-NAVA were on levels ranging from 1 to 2 cmH_2O/µV, while breakpoints were on average 0.66 cmH_2O/µV higher. This might reflect suboptimal unloading of respiratory effort and three patients subsequently needed to be intubated due to respiratory failure. Further research is needed to investigate whether the use of higher initial NAVA levels aiming at optimal unloading is superior to the current approach. Caution is warranted, however, because of a possible risk of overdistension of the premature lung with higher NAVA levels due to immature feedback mechanisms. Our advice for clinical practice would be to intensively monitor premature infants who are supported with NIV-NAVA both for hypo- and hyperventilation. We should remain aware of the possibility that also non-invasive ventilatory support might cause ventilator-induced lung injury. But it seems that even in (extremely) preterm infants with RDS, NIV-NAVA is feasible. When starting NIV-NAVA, we suggest

to start with higher NAVA levels and titrate the NAVA level to the clinical and ventilatory (PIP and Edi) response. But larger trials will be needed to more thoroughly investigate diaphragmatic function and NAVA ventilation in preterm infants with RDS, before formulating formal recommendations about the use of NIV-NAVA in this population.

RR decreased significantly with on average nine breaths per minute during the study. This reflects a decrease in work of breathing. There were no significant changes in HR, SpO_2 and FiO_2 detected. Two patients showed short and mild desaturation with minimum SpO_2 of 86% for 30 s. We could therefore conclude that the titration protocol was well tolerated.

A limitation of the study is the small number of patients. This study served as a pilot study for a future larger clinical trial on NIV-NAVA. Due to the small sample size and the large intra- and interpatient variability in Edi and RR the statistical analyses are vulnerable to outliers. Furthermore, because each patient was measured intensively for RR, even the smallest within patient change was detected, so we focused on the average change in RR over time. Another limitation of the analyses on RR, HR and SpO_2 in relation to the changing NAVA levels is that they are possibly confounded with time, as their order was the same for all patients. We did not look for the effect of a specific NAVA level or change in NAVA level on these parameters.

Although the goal of the study was to have a homogeneous study population of preterm infants with acute RDS, some of the infants might have been in another stage or severity of RDS as reflected by the postnatal age at study day and the use of surfactant.

Another limitation is that the visual inspection of the curves for identifying the breakpoint was prone to subjective error, as shown by the fact that some of the breakpoints had to be adjusted after statistical analysis. This raises questions about the reproducibility of the breakpoint and of its possible use as a clinical tool.

Information on partial carbon dioxide pressures and tidal volumes is lacking. The effect of changing NAVA levels on alveolar minute ventilation remains therefore unknown.

Conclusions

This study showed that preterm infants also in their early phase of RDS have a similar pattern of respiratory unloading as previously described in preterm infants at an older age and with other conditions. The levels at which maximal respiratory unloading was achieved during NIV-NAVA were higher than the levels that are commonly used in this clinical situation. Neural feedback mechanisms seem to be immature with the risk of insufficient support with lower NAVA levels and lung injury due to overdistension of the lung in higher NAVA levels. NIV-NAVA can be used in preterm infants with RDS but careful monitoring is warranted.

Further studies are needed to evaluate the possible benefits and safety of the use of optimized NAVA levels in this population, both on short-term as well as on long-term clinical outcomes.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00431-021-04244-3.

Authors' contributions JL and FC contributed to the study conception and design. Material preparation and data collection were performed by JL and BVD. Data analysis was performed by JL, MV and WC. The first draft of the manuscript was written by JL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Data can be made available upon request.

Declarations

Ethics approval The UZ Brussel medical ethics committee approved the study and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Signed written informed consent by the parents of the study participants was obtained prior to inclusion in the study.

Conflict of interest The authors declare no competing interests.

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