Journal of Perinatology (2020) 40:1211–1215
https://doi.org/10.1038/s41372-020-0661-x

ARTICLE

Nasal continuous positive airway pressure versus noninvasive NAVA in preterm neonates with apnea of prematurity: a pilot study with a novel approach

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Received: 4 January 2020 / Revised: 2 March 2020 / Accepted: 11 March 2020 / Published online: 26 March 2020

Abstract

Background Neonates with apnea of prematurity often fail CPAP because it does not provide adequate support during apnea. NAVA provides proportional ventilator support based on electrical activity of the diaphragm. When the NAVA level is 0 cmH_20/mcV, the patient receives minimal support above PEEP when breathing and backup ventilation when apneic. This study compares number of clinically significant events on CPAP versus noninvasive NAVA level 0.

Methods Retrospective study of preterm neonates having apnea of prematurity on nasal CPAP. Patients were then placed on NAVA level 0. The number of events on each mode was collected. Statistics were paired *t*-test.

Results Seventeen subjects with gestational age 26.1 ± 1.7 weeks, study age 19.5 ± 12.5 days. Events decreased from 17.9 ± 7.8 on CPAP to 10.2 ± 8.1 events on NAVA level 0 ($p = 0.00047$).

Conclusions NAVA level 0 reduced the number of clinically significant events compared with CPAP in premature neonates with apnea of prematurity.

Introduction

Apnea of prematurity (AOP) remains a challenge in preterm neonates and the severity of AOP is correlated inversely with gestational age [1]. All preterm neonates born less than 28 weeks gestation have apnea, 85% at 30 weeks gestation, and 20% at 34 weeks gestation [2]. Current treatment of AOP is administration of caffeine citrate and if the apnea remains significant, nasal constant positive pressure (nCPAP) is initiated followed by invasive ventilation if it is deemed to be severe apnea [1, 3].

CPAP provides constant pressure throughout respiration, controlled by the demand-flow system in the expiratory valve to help spontaneous breathing in preterm neonates [4]. When neonates with AOP are breathing spontaneously, CPAP is sufficient to support their ventilatory effort. However, during periods of apnea, as seen in Fig. 1, no additional support is provided and the neonate is susceptible to clinically significant events (CSE) characterized by desaturations and bradycardia. Increasing support to non-invasive pressure support ventilation (NIV-PS) allows backup ventilation when no flow is detected and setting the pressure support at 0 cmH_2O should provide no additional pressure support (CPAP only) during spontaneous ventilation and backup support when apneic. However, as seen in Fig. 2, the flow trigger with NIV-PS is unreliable and backup breaths occur during spontaneous respiration and the ventilator fails to provide backup support when the neonate is apneic.

Noninvasive neurally adjusted ventilatory assist (NIV NAVA) allows patients to control their own peak inspiratory pressure and tidal volume on a breath-to-breath basis [5]. It is delivered with the Servo-I/U ventilator (Getinge, Germany) with NIV NAVA software. A specialized nasogastric tube is placed at the level of the crural diaphragm and embedded electrodes detect the electrical activity of the diaphragm (Edi). Positive pressure is then delivered for the duration of, and in proportion to, the amount of electrical activity detected. The NAVA level is a

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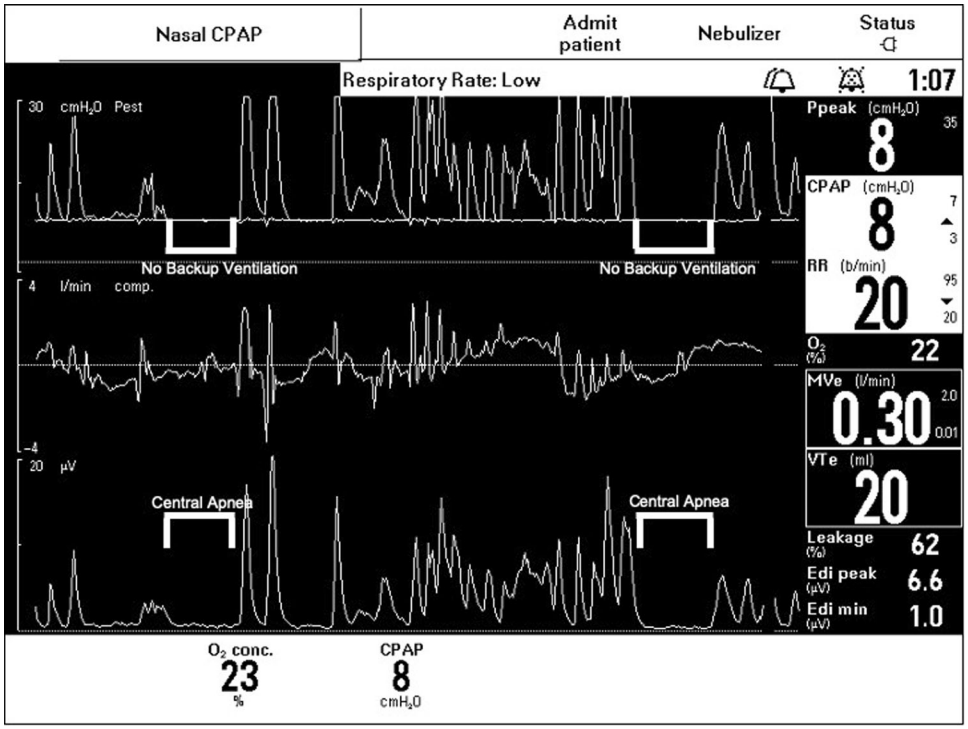

Fig. 1 Periods of apnea while on CPAP. The bottom line is the Edi signal. The middle line is flow. The top line is pressure with the pressure estimate (derived from the Edi signal) superimposed. The patient gets CPAP when both breathing and when apneic.

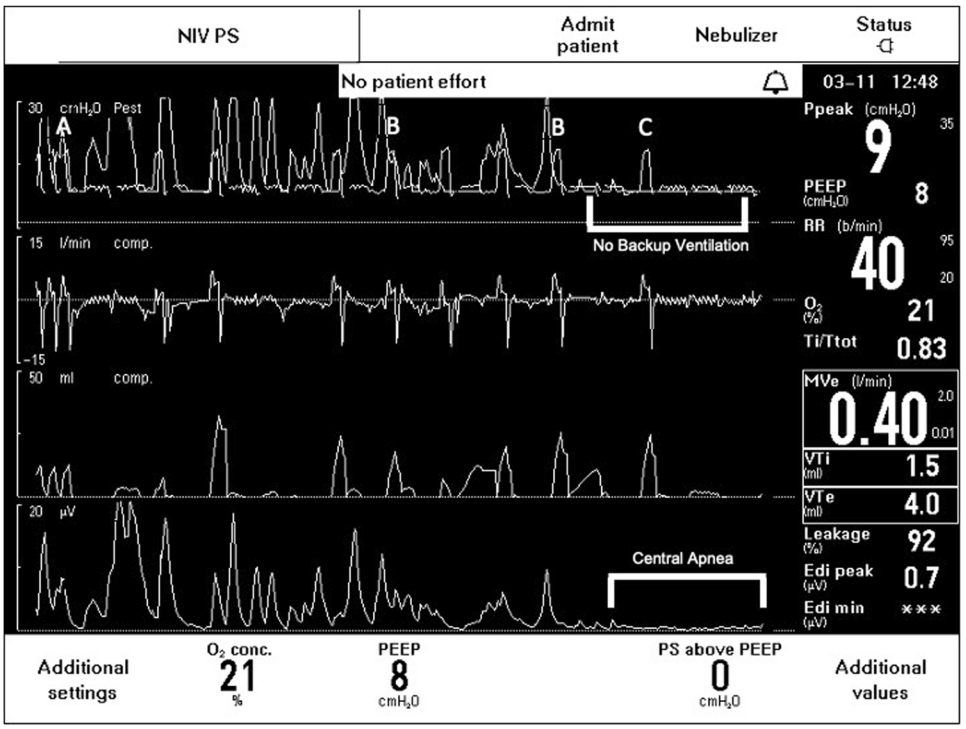

Fig. 2 Period of apnea when on noninvasive pressure support ventilation. The bottom line is the Edi signal. The next line up is volume and the third line up is flow. The top line is pressure with the pressure estimate (derived from the Edi signal) superimposed. The patient gets pressure support breaths when both breathing and apneic. These are not synchronized with some breaths autotriggering (**a**), some occurring during expiration (**b**), and provides minimal support when apneic (**c**).

proportionality constant that converts the Edi into a delivered inspiratory pressure above PEEP [6]. If the neonate becomes apneic for a predetermined amount of time (apnea time), pressure control backup ventilation is provided until spontaneous ventilation, as detected by the Edi, resumes. Setting the NAVA level at 0 cmH_2O/mcV when on NIV NAVA (NN0), as seen in Fig. 3, has been proposed as an alternate method to deliver CPAP with backup ventilation in neonates who are failing CPAP due to AOP [5, 7].

This pilot study compares the number of CSE in neonates who were failing CPAP due to AOP with the number of CSE on NN0.

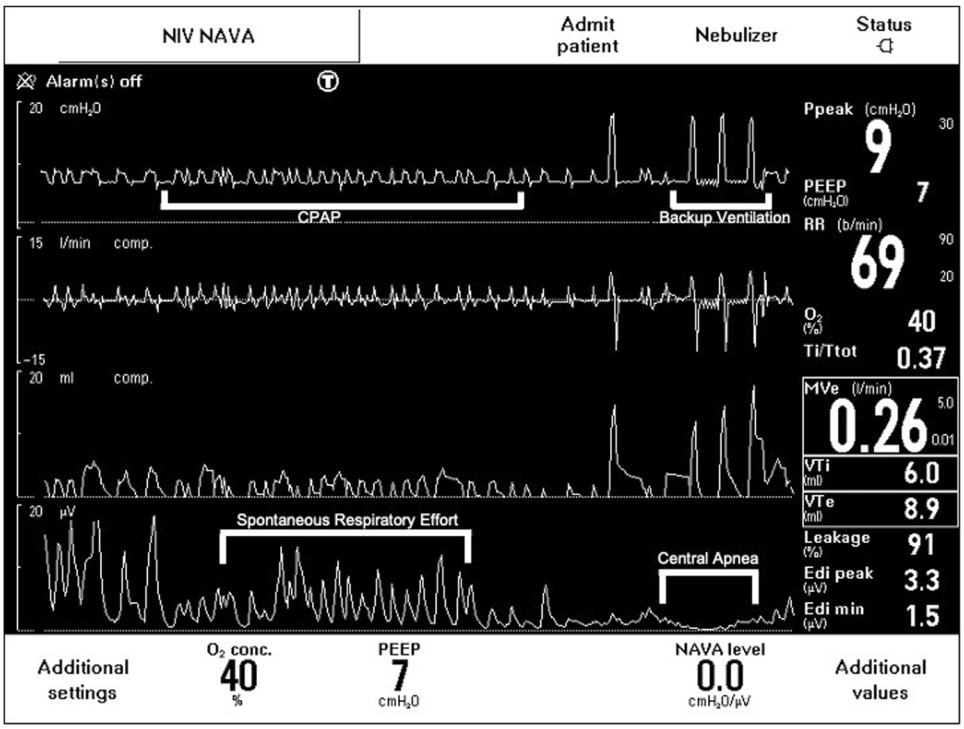

Fig. 3 Period of apnea when on noninvasive NAVA. The bottom line is the Edi signal. The next line up is volume and the third line up is flow. The top line is pressure. The patient gets minimal support above CPAP when breathing and backup ventilation when apneic. Autotriggering does not occur as neural triggering is the mechanism for initiation.

Methods

This was a single-center retrospective study of neonates admitted to the neonatal intensive care unit at ProMedica Toledo Children's Hospital between 9/2015 and 12/2017. IRB approval was obtained. Neonates that were previously supported with nCPAP with a significant number of CSE, and changed at the discretion of the treating physician to NN0 were identified. CSE were defined as apnea lasting more than 20 s, apnea for more than 10 s accompanied by bradycardia (<80 bpm), or desaturation (<90%). When switched to NN0, PEEP remained at the previous CPAP pressure level and the Servo-I/U delivers a PIP of 2 cmH_20 above PEEP for each spontaneous breath. Backup settings, which included backup PIP, pressure limit, and apnea time, were chosen by the treating physician. CSE were collected retrospectively from the nurses' electronic data charting, for 24 h on nCPAP and then for the following 24 h on NN0. Demographic data and ventilator settings were collected. Paired *t*-test was used to compare the number of CSE on CPAP versus NN0.

Results

Seventeen subjects were enrolled in the study. Table 1 shows demographics of the subjects. All neonates had AOP and all were being treated with caffeine. Caffeine was dosed at 10 mg/kg/day and caffeine levels were not monitored.

Table 1 Demographics of the study subjects.

Number of subjects	17 (10 females)
Gestational age at birth	26.1 ± 1.7 weeks (range 23–29)
Birth weight	877 ± 164 g (range 630–1210)
Median Apgar scores	4 (1 min), 8 (5 min)
Prenatal steroids	94%
Surfactant	88%
Age at study	19.5 ± 12.5 days (range 4–45)
Weight at study	914 ± 224 g (range 555–1435)
IVH (grade III–IV)	18%
NEC	6%
ROP	12%
CLD	24%

Ages and weights are average ± SD.

IVH intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *CLD* chronic lung disease.

The median CPAP was 7 (range 5–9) cmH_2O. PEEP on NN0 was exactly the same as CPAP. On NN0 the average backup PIP was 19 (range 16–21) cmH_2O, median peak pressure limit was 35 (range 30–40) cmH_2O, median apnea time was 2 s (range 2–5 s). Both CPAP and NN0 were delivered by RAM cannula (Neotech, Los Angeles, CA). Figure 4 shows the average number of CSE over 24 h decreased from 17.9 ± 7.8 on CPAP to 10.2 ± 8.1 events on NAVA level 0 (paired *t*-test with normal distribution of the data, $p = 0.00047$).

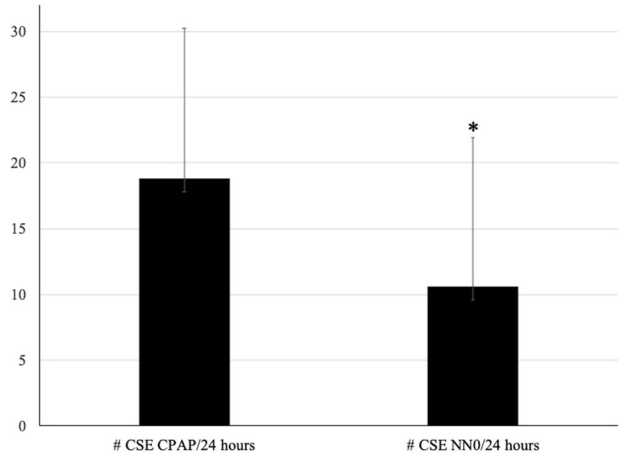

Fig. 4 Clinically significant events CSE were defined as apnea lasting more than 20 s, apnea for more than 10 s accompanied by bradycardia (<80 bpm) or desaturation (<90%). Average CSE decreased from CPAP to NN0 over a 24 h period (an asterisk indicates paired *t*-test with normal distribution of the data, $p = 0.00047$).

Discussion

NN0 is the only mode currently available to deliver CPAP when breathing and backup ventilation when apneic. This pilot study showed the efficacy of this approach, in that NN0 decreased the number of CSE in premature neonates compared with using CPAP.

Tabacura et al. recently showed that noninvasive NAVA decreased the number of CSE compared with nonsynchronized noninvasive ventilation [8]. In this study, both modalities provide noninvasive ventilatory support, which has both short and long term associated risks [9]. Our study suggests it may be possible to treat CSE with a less invasive strategy that provides CPAP (NN0) when the neonate is breathing and noninvasive ventilation only when apneic. This approach may have the benefit of reducing CSE while minimizing exposure to noninvasive ventilation and reducing associated morbidities of noninvasive ventilation.

When NIV NAVA is set at 0 cmH_20/mcV the Servo-I/U delivers a PIP of 2 cmH_20 above PEEP. The neonates therefore are actually receiving PEEP plus 2 cmH_20 for each spontaneous breath, the set PIP for each backup breath and set PEEP in between all these breaths. It is therefore possible that the overall benefit of NN0 is to deliver a slightly higher mean airway pressure and it is this increased pressure that causes the decrease in CSE and not the backup ventilation that is provided when the neonates are apneic. To further explore these reasons for this reduction in CSE, prospective studies would be needed to compare CPAP with various levels of PEEP when on NN0.

The apnea time setting on the Servo-I/U is the duration of respiratory pause (no Edi signal) after which the ventilator delivers a set backup breath. This allows the clinician to set a minimum respiratory rate. Morgan et al. have shown that apnea times of 2 s (minimum rate of 30 breaths/min) results in less CSE compared with apnea times of 5 s (minimum rate of 12 breaths/min) [10]. Although most neonates in the present study were on an apnea time of 2 s, a few were on longer apnea times. Had all neonates been on apnea time of 2 s it was possible that the number of CSE could have been reduced further.

Chronic lung disease, retinopathy of prematurity, and interventricular hemorrhage were higher in this study population than historically seen in this center. These data could be skewed by 6 of the 17 neonates being 23–25 weeks, but the small number of neonates enrolled prevented any meaningful comparisons.

The major weakness of this study is that it is retrospective and presents several study limitations. It was not possible to evaluate the number of times the neonate went into backup ventilation and the amount of time spent in backup during the study period. Neither of these parameters are recorded in the medical record and it is not possible to obtain these data retrospectively. Knowing this information would allow determination if the neonates were having brief respiratory pauses (frequent switches to backup but minimal time in backup) or apnea (few switches to backup but longer periods in backup). Another limitation is the lack of randomization of treatment epochs between CPAP and NN0. This would address the possibility that the decrease in CSE is due to 24 h of maturation in these neonates and a similar result could have been noted if the neonates had remained on CPAP. It is also possible that it was not NN0 itself but a change to another mode of ventilatory support that resulted in improvement in number of CSEs. Larger prospective studies are needed to address the limitations of this small, retrospective study and to evaluate if the use of NN0 in these neonates failing CPAP due to CSE may prevent escalation to noninvasive or invasive ventilation thereby decreasing long term morbidity and length of stay.

Conclusion

NIV NAVA 0 reduced the number of CSE compared with nCPAP in premature neonates with apnea. Despite not knowing if this due to an overall increased mean airway pressure or due to providing backup ventilation, or if this approach treats brief respiratory pauses or apnea, the pragmatic view is that there are less CSE when treated with NN0 compared with when using nCPAP. Based on these preliminary data, it is suggested that prospective trials be performed to evaluate if NIV NAVA 0 can offer a safe and

effective option for the treatment of neonates failing CPAP due to frequent desaturations and bradycardia.

Author contributions HS, LB, and KF contributed to the study design. HS, LB, and BAH contributed to data collection. All authors contributed in writing the manuscript.

Compliance with ethical standards

Conflict of interest HS and KF are on the speakers' bureau for Getinge and Chiesi USA Inc. BAH and LB have nothing to disclose.

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