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Fluctuations in Oxygen Saturation during Synchronized Nasal Intermittent Positive Pressure Ventilation and Nasal High-Frequency Oscillatory Ventilation in Very Low Birth Weight Infants: A Randomized Crossover Trial

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Keywords
Preterm infant · Oxygen saturation target · Nasal intermittent positive pressure ventilation · Nasal high-frequency oscillatory ventilation · Desaturation · Hypoxemia

Abstract
Background: Very low birth weight (VLBW) infants on non-invasive ventilation (NIV) experience frequent fluctuations in oxygen saturation (SpO_2) that are associated with an increased risk for mortality and severe morbidities. ***Methods:*** In this randomized crossover trial, VLBW infants (n = 22) born 22+3 to 28+0 weeks on NIV with supplemental oxygen were allocated on two consecutive days in random order to synchronized nasal intermittent positive pressure ventilation (sNIPPV) and nasal high-frequency oscillatory ventilation (nHFOV) for 8 h. nHFOV and sNIPPV were set to equivalent mean airway pressure and transcutaneous pCO_2. Primary outcome was the time spent within the SpO_2 target (88–95%). ***Results:*** During sNIPPV, VLBW infants spent significantly more time within the SpO_2 target (59.9%) than during nHFOV (54.6%). The proportion of time spent in hypoxemia (22.3% vs. 27.1%) and the mean fraction of supplemental oxygen (FiO_2) (29.4% vs. 32.8%) were significantly reduced during sNIPPV, while the respiratory rate (50.1 vs. 42.6) was significantly higher. Mean SpO_2, SpO_2 above the target, number of prolonged (>1 min) and severe (SpO_2 <80%) hypoxemic episodes, parameters of cerebral tissue oxygenation using NIRS, number of FiO_2 adjustments, heart rate, number of bradycardias, abdominal distension and transcutaneous pCO_2 did not differ between both interventions. ***Conclusions:*** In VLBW infants with frequent fluctuations in SpO_2, sNIPPV is more efficient than nHFOV to retain the SpO_2

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target and to reduce FiO_2 exposure. These results demand more detailed investigations into cumulative oxygen toxicities during different modes of NIV over the weaning period, particularly with regard to consequences for long-term outcomes.

Introduction

Very preterm (VLBW) infants get exposed to a hyperoxic environment ex utero, but the fraction of inspired oxygen (FiO_2), as well as the exposure time vary greatly, which dramatically impacts the extent of injuries in preclinical models [1, 2]. Reactive oxygen species production is boosted by hyperoxia but also by hypoxemia with subsequent reoxygenation [3, 4]. This latter finding is of utmost importance as preterm infants experience a magnitude of hypoxemic events, particularly when breathing spontaneously, and their antioxidative defense mechanisms are poorly developed [5]. Association studies linked the amount and severity of fluctuations in oxygen saturation (SpO_2) to all important outcomes, including mortality, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and impaired psychomotor development [3, 4, 6]. Hence, SpO_2 targeting has become a research priority.

With the improvements in noninvasive ventilation (NIV) and surfactant application, fewer VLBW infants require invasive mechanical ventilation. These advances aim to reduce the BPD burden, but hyperoxic and hypoxemic episodes pose a therapeutic challenge that cannot be solely tackled by medication treating central apneas [1, 5]. Continuous positive airway pressure (CPAP) is still the best-studied form of NIV and experimental studies demonstrated that CPAP efficiently reduces the oxidative burden as well as lung injuries [7]. Newer modes of NIV, like nasal intermittent positive pressure ventilation (NIPPV) or nasal high-frequency oscillatory ventilation (nHFOV), were introduced into daily clinical practice to improve its efficacy. NIPPV was shown to be superior to CPAP as primary ventilatory support to avoid mechanical ventilation or as the first-line mode after extubation. NIPPV is more efficient when applied in a synchronized (sNIPPV) manner [8]. nHFOV decreases the risk of intubation compared to CPAP when used as primary respiratory support and post-extubation [9, 10]. But neither sNIPPV nor nHFOV had a positive effect on the important outcomes of prematurity compared to CPAP [8, 9]. One study in more mature infants demonstrated no difference in extubation failure between NIPPV and nHFOV, but nHFOV was more efficient in CO_2 elimination [11]. Based on these studies, proponents of nHFOV argue its application in NICU during the weaning process.

Primary aim of this randomized crossover study was to establish whether sNIPPV or nHFOV was better suited to maintain SpO_2 within a preset target range in respiratory unstable VLBW infants on NIV with supplemental oxygen. Further analyses were focused on the number and duration of hypoxic and hyperoxic episodes.

Methods

Study Population

All preterm infants <32 weeks with a birth weight <1,500 g and postnatal age >72 h at the tertiary level NICU of the perinatal center Giessen on sNIPPV without: severe congenital malformations, scheduled blood transfusion or surgical interventions, treatment for bacterial infection for the last 72 h before study entry and escalation of NIV for desaturations <70% for >1 min or bradycardias <100/min for >30 s within 12 h prior to study entry were considered eligible for this randomized crossover trial. Prerogative for study inclusion was the persistent dependency on NIV with a positive end-expiratory pressure (PEEP) ≤8 cmH_2O, need for supplemental oxygen ≤60% and at least four hypoxemic episodes with SpO_2 <80% for >30 s within the last 12 h before study entry documented in the electronic monitoring system.

Study Design

Using sealed envelopes, infants were randomly assigned to start with sNIPPV or nHFOV using a Sophie respirator (Fritz Stephan GmbH, Gackenbach, Germany) for 8 h. Blinding of the interventions was not feasible. The second observation period was started the next day at around the equivalent time as during the first study phase. CPAP was used prior and between the two interventional periods to minimize carryover effects with the use of sNIPPV or nHFOV (shown in Fig. 1). The sNIPPV settings during the study were as during sNIPPV before CPAP wash-out with an inspiratory time of 0.3 s and a mandatory synchronized rate of 40/min (SIMV-mode). The Graseby capsule was placed in subxiphoid position as recommended to allow synchronization during NIPPV. Reaction time of the Grasby capsule is 50 msec and synchronization rate >80% in comparable settings [12]. Mean airway pressure (MAP) during nHFOV was set as during sNIPPV before study entry or during the first intervention period depending on the allocated sequence of NIV. Oscillation amplitude was started at 20 cmH_2O, 40% inspiration:expiration ratio and a frequency of 10 Hz. nHFOV amplitude was adapted to reach identical transcutaneous pCO_2 as during sNIPPV. Either prongs or mask were used as CPAP interface and infants were kept identically in prone or supine position during both study phases at the discretion of the attending nurse. The mouth was not closed with a chin strap. Parents were allowed to kangaroo care for up to 50% of the observation period. Data were continuously recorded without interruption during infant handling. The SpO_2 target was kept at the NICU standard of 88–95%.

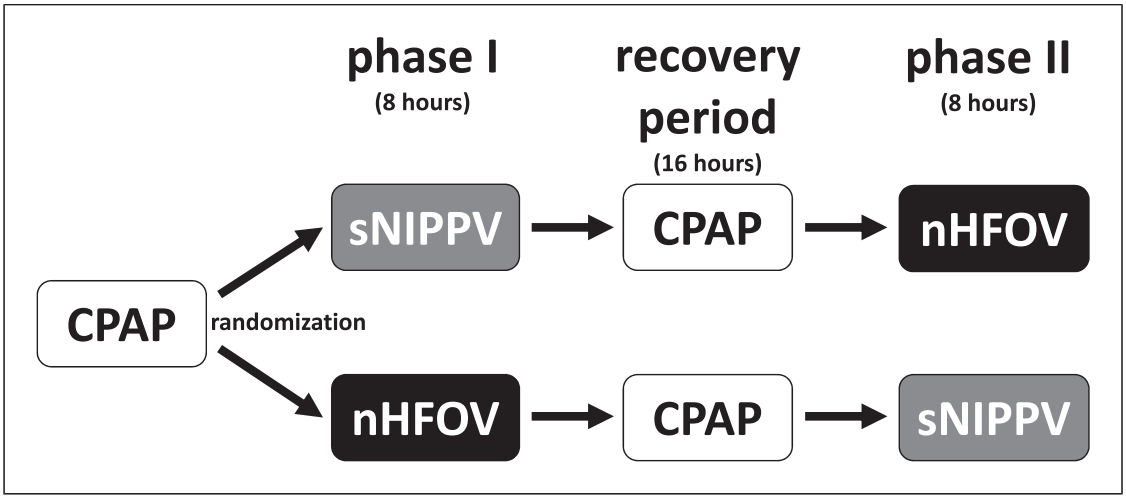

Fig. 1. Study outline of the randomized crossover trial on sNIPPV and nHFOV. Sequence of interventions for 8 h on two consecutive days was determined by randomization. Study entry was preceded by baseline CPAP and a recovery period on CPAP was inserted between the interventions. sNIPPV, synchronized nasal intermittent positive pressure ventilation; nHFOV, nasal high-frequency oscillatory ventilation; CPAP, continuous positive pressure ventilation.

Physicians and nurses were advised to a standard protocol of FiO_2 adjustment as published [13]. The nurse-to-patient ratio was at least 1:2. All routine co-interventions including feeding intervals and medical therapy of apnea with caffeine citrate and doxapram remained unchanged during the total study period. The criteria for study discontinuation (start of invasive mechanical ventilation at the discretion of the attending physician, respiratory acidosis with a pH <7.1 in two subsequent blood gas analyses or necrotizing enterocolitis) were not fulfilled in any participant.

Primary and Secondary Endpoints and Sample Size Calculation

The primary outcome was time spent within the SpO_2 target (SpO_2 88–95%). Time spent above the SpO_2 target was not taken into account for hyperoxemia calculation when the infant was breathing room air. Sample size calculation was based on the findings from a previous study displaying a 7.5% difference [13]. Assuming comparable clinically relevant differences between sNIPPV and nHFOV, a sample size of 18 patients was calculated using a two-sided paired *t* test with an inner subject variance of 81, a two-sided type one error of 0.05 and α power of 0.90. To account for dropouts due to insufficient data recording quality, patient consent withdrawal and nonparametric parameter distribution, the sample size was increased by 33% to 24 patients. All statistical tests with exception for the primary endpoint were performed in an exploratory manner and have to interpreted as hypothesis generating only and not as confirmatory. An adjustment for multiple testing was not made.

Secondary outcomes included the time spent in hypoxemia (SpO_2 <88%), in severe hypoxemia (SpO_2 <80%), and in iatrogenic hyperoxemia (SpO_2 >95% with FiO_2 >0.21). Additionally, the number of hypoxemic (SpO_2 <88%) and severe hypoxemic (SpO_2 <80%) and of bradycardia episodes (<100/min) for ≥30 s, ≥60 s, and ≥120 s, of FiO_2 adjustments, mean cerebral tissue oxygen saturation ($SctO_2$) and time of $SctO_2$ <65% and <60% were evaluated. Furthermore, the mean SpO_2, respiratory frequency, heart rate, transcutaneous pCO_2 and FiO_2 during each study phase were calculated.

Data Collection and Recording

Baseline demographic parameters were recorded and definitions used as described [14]. Silverman score and abdominal circumference measured 1 cm above the navel were recorded before and after the intervention. The SpO_2 sensor was attached to the right upper extremity. SpO_2, heart rate, and respiratory frequency were recorded from an IntelliVue MP50 monitor (Philipps, Amsterdam, The Netherlands, SpO_2 averaging time 8 s). Ventilation parameters and FiO_2 were retrieved from the respirator and any adjustment documented. Continuous measurement of $SctO_2$ by near-infrared spectroscopy was executed using a Root kit 3.0 device (Massimo, CA). Signals were recorded at 2-s intervals into separate data folders of a specifically developed software solution with a time stamp and the option to mark events including kangaroo care, patient rounds, and dislocation of the CPAP device.

Statistical Analysis

Patients with data acquisition for <75% of recording time in either of the study arms were excluded from the analyses. Continuous variables were described as mean and standard deviation or median and quartiles. Categorical variables were reported as absolute and relative frequencies. For continuous variables, the paired *t* test or Wilcoxon signed-rank test, as appropriate, was used for statistical comparisons. A two-sided *p* value ≤0.05 was considered to be statistically significant. Statistical analyses were performed using Sigma Plot (Systat Software Inc., CA) version 12.3 and R, version 4.1.2.

Table 1. Baseline characteristics of patients included in the study (n = 22)

Patient characteristics	Values
Gestational age, weeks	25 + 4 (22+3 to 28+0)
Birth weight, g	645 (330–1,440)
Small for gestational age (<10th percentile), *n* (%)	3 (13.6)
Male gender, *n* (%)	9 (40.9)
Multiple birth, *n* (%)	6 (27.3)
Maternal age, years	32.5 (22.0–42.0)
Gravidity	3 (1–6)
Antenatal steroids before birth, *n* (%)	22 (100.0)
Antenatal steroids ≤48 h before birth, *n* (%)	6 (27.3)
Antenatal steroids >48 h to ≤7 days before birth, *n* (%)	12 (54.5)
Antenatal steroids >7 days before birth, *n* (%)	4 (18.2)
Preeclampsia/HELLP, *n* (%)	3 (13.6)
Chorioamnionitis, *n* (%)	8 (36.4)
PPROM, *n* (%)	12 (54.6)
Mode of delivery C-section, *n* (%)	22 (100.0)
Umbilical cord pH	7.28 (6.60–7.40)
APGAR 1 min	7 (0–9)
APGAR 5 min	8 (4–10)
APGAR 10 min	9 (5–10)
Surfactant therapy, *n* (%)	22 (100.0)
Doses of surfactant	1 (1–2)
Postnatal corticosteroids <7 days after birth, *n* (%)	0 (0.0)
Postnatal corticosteroids >7 days after birth, *n* (%)	3 (13.6)
Diuretic therapy, *n* (%)	0 (0.0)
Invasive mechanical ventilation, days	1.0 (0.0–45.0)
Noninvasive respiratory support, days	64.5 (36.0–113.0)
Oxygen supplementation, days	57.0 (4.0–127.0)
No BPD, *n* (%)	4 (18.2)
Mild BPD, *n* (%)	9 (40.9)
Moderate BPD, *n* (%)	3 (13.6)
Severe BPD, *n* (%)	6 (27.3)
Intraventricular hemorrhage (any grade), *n* (%)	1 (4.6)
Focal intestinal perforation, *n* (%)	2 (9.1)
Necrotizing enterocolitis, *n* (%)	0 (0.0)
Retinopathy of prematurity (any grade), *n* (%)	15 (68.2)
Retinopathy of prematurity (therapy), *n* (%)	2 (9.1)

Data are presented as median and range or *n* (%). If antenatal steroids had been applied >7 days before delivery, a boost was given intravenously immediately before delivery. PPROM, preterm premature rupture of membranes; C-section, caesarian section; BPD, bronchopulmonary dysplasia.

Results

Patient Characteristics

Data sets from 22 VLBW infants with a median gestational age of 25+4 weeks (range 22+3 to 28+0) at birth and a median postnatal age of 26.5 days (range 10.0–84.0) at study inclusion were available for analysis. Records from 2 patients did not fulfill the prespecified criteria. Further patient baseline characteristics are presented in Table 1. The mean pre-study PEEP was 5.8 (5.0–8.0) cmH_2O and FiO_2 0.26 (0.23–0.45) (Table 2). Allocation to the intervention sequences was balanced with 11 infants each first assigned to sNIPPV or nHFOV. Overall, 14 of 22 caregivers made use of the option for kangaroo care and time periods did not differ significantly between both study phases (Table 3).

SpO_2 Fluctuations during sNIPPV and nHFOV

MAP and transcutaneous pCO_2 did not differ between both interventions creating comparable conditions of respiratory support. The primary outcome of SpO_2 within the target was significantly higher during

Table 2. Respiratory status of patients at inclusion into the study (n = 22)

Study entry characteristics and NIV settings	Values
Gestational age at study entry, weeks	29+0 (27+1 to 35+3)
Postnatal age at study entry, days	26.5 (10.0–84.0)
Weight at study entry, g	1,035 (640–2,480)
Pre-study PEEP, cmH_2O	5.8 (5.0–8.0)
Pre-study FiO_2	0.26 (0.23–0.45)
Caffeine therapy, n (%)	22 (100.0)
Caffeine dosage, mg/kg/day	20.0 (7.5–25.0)
Doxapram therapy, n (%)	5 (22.7)
Doxapram dosage, mg/kg/day	21 (14–23)
sNIPPV parameters during intervention	
PIP, cmH_2O	15.5 (15.0–18.0)
MAP, cmH_2O	7.5 (6.5–9.3)
PEEP, cmH_2O	5.5 (5.0–8.0)
NIPPV frequency (1/min)	40 (40–40)
Inspiratory time, seconds	0.30 (0.30–0.30)
nHFOV parameters during intervention	
MAP, cmH_2O	7.5 (5.0–10.0)
Posz, cmH_2O	20 (20–30)
i:e ratio (%)	40 (40–40)

Data are presented as median and range or n (%). FiO_2, fraction of inspired oxygen; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; Posz, oscillatory amplitude; i:e ratio, inspiratory to expiratory time.

sNIPPV compared to nHFOV (Table 3, shown in Fig. 2). An individual patient analysis revealed that 16 out of 22 spent more time in the SpO_2 target during sNIPPV.

Secondary Outcome Measures during sNIPPV and nHFOV

For the secondary outcomes, the percentage of time spent in hypoxemia and the mean FiO_2 were assessed and found to be significantly lower during sNIPPV than nHFOV, while the mean SpO_2, the number and duration of severe hypoxemic episodes (SpO_2 <80%) per hour of recording using subcategorizing criteria, the total duration in hyperoxemia, number of bradycardic episodes, and the number of manual FiO_2 adjustments did not differ between both interventions (Table 3; shown in Fig. 2). As the time spent with SpO_2 <70% was very low in our study population (1.5 ± 0.3% for sNIPPV vs. 1.2 ± 0.3% for nHFOV), we did not detail these analyses. In contrast to the SpO_2 measurements, there was no significant difference in the mean $SctO_2$ and the proportion of time spent with $SctO_2$ <65% and <60%. $SctO_2$ <55% represented a rare event in both intervention arms (<0.2% of the time). The mean respiratory frequency was significantly lower during nHFOV, while mean heart rate, Silverman score and abdominal circumference did not differ between the groups (Table 3).

Discussion

The association of fluctuations in SpO_2 with impaired neurodevelopmental outcome, ROP and BPD is supported by large multicenter studies [3, 4, 6]. Preterm infants are particularly vulnerable for desaturations followed by reoxygenation when on NIV [15]. This sequence boosts ROS production with increased risk for ROS-related diseases [5, 6]. In this randomized crossover study, sNIPPV proved superior in maintaining SpO_2 within a predefined target range when compared to nHFOV. Furthermore, our data indicate a tendency that sNIPPV better prevents the outcome relevant events of prolonged and severe hypoxemias [4, 6]. This efficacy was not achieved at the expense of increased hyperoxemia, higher FiO_2, or more manual FiO_2 adjustments. The increased remaining within the SpO_2 target range during sNIPPV even enabled reduced mean FiO_2 requirements while higher mean FiO_2 during nHFOV might be due to the tolerance of the NICU staff when faced with more time spent outside the oxygen saturation target range [1, 5].

NIV is the primary method of respiratory support in the delivery room and standard of care during weaning after extubation. Therefore, every preterm infant is exposed to at least one mode of NIV for a shorter or longer period during the stay in the NICU. For the established NIV modes, actual meta-analyses favor sNIPPV compared to CPAP [16, 17]. During recent years, several new

Table 3. Comparison of outcome measures between sNIPPV and nHFOV (n = 22)

Variables	sNIPPV	nHFOV	p value
Time (%) within the SpO_2 target (88–95%)	59.6 (11.1)	54.7 (10.0)	**0.020**[a]
Time (%) below the SpO_2 target (<88%)	22.3 (5.8)	26.9 (6.8)	**0.015**[a]
Time (%) above the SpO_2 target (>95%)	18.2 (9.5)	18.4 (12.3)	0.891[a]
Time (%) SpO_2< 80%	7.4 (2.8–13.4)	8.9 (5.3–14.9)	0.495[b]
Time (%) SpO_2< 70%	1.5 (0.26)	1.2 (0.33)	0.570[a]
Mean SpO_2 (%)	90 (90–91)	90 (89–91)	0.190[b]
Mean $SctO_2$ (%)	67.6 (5.2)	66.2 (5.3)	0.073[a]
Time (%) of $SctO_2$ <65%	18.1 (5.7–44.5)	19.7 (9.9–50.8)	0.436[b]
Time (%) of $SctO_2$ <60%	2.2 (0.5–8.7)	2.2 (0.9–10.5)	0.270[b]
Hypoxemias (<88%) ≥30 s/h	4.1 (3.3–4.6)	4.8 (4.1–5.9)	0.0501[b]
Hypoxemias (<88%) ≥60 s/h	2.3 (1.6–2.9)	2.9 (2.3–3.4)	0.0587[b]
Hypoxemias (<88%) ≥120 s/h	0.6 (0.3–0.7)	0.8 (0.6–1.2)	**0.010**[b]
Severe hypoxemias (<80%) ≥30 s/h	0.6 (0.3–1.6)	1.1 (0.7–2.0)	0.054[b]
Severe hypoxemias (<80%) ≥60 s/h	0.3 (0.1–0.4)	0.4 (0.2–0.6)	0.118[b]
Severe hypoxemias (<80%) ≥120 s/h	0.0 (0.0–0.1)	0.2 (0.1–0.2)	0.851[b]
Bradycardias (<100/min) ≥10 s/h	0.2 (0.0–0.5)	0.0 (0.0–0.2)	0.093[b]
Mean FiO_2 during intervention	0.30 (0.26–0.33)	0.33 (0.27–0.39)	**0.006**[b]
Manual FiO_2 adjustments/h	1.8 (1.9)	2.8 (2.5)	0.135[a]
Mean $tcpCO_2$, mm Hg	59.5 (7.7)	60.4 (7.0)	0.333[a]
Mean airway pressure (MAP, cmH_2O)	7.5 (6.5–8.2)	7.5 (6.5–8.2)	0.297[b]
Respiratory rate (1/min)	50.0 (9.9)	42.5 (10.2)	**0.004**[a]
Heart rate (1/min)	167.8 (10.5)	168.6 (10.5)	0.316[a]
Time spent with kangaroo care, min	72.9 (16.9)	80.9 (15.7)	0.702[a]
Abdominal circumference at 0 h, cm	25.4 (3.4)	25.6 (3.1)	0.485[a]
Abdominal circumference at 8 h, cm	25.9 (3.6)	25.8 (3.2)	0.447[a]
Silverman score at 0 h	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.095[b]
Silverman score at 8 h	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.465[b]

Hypoxemia is defined as SpO_2 <88%, severe hypoxemia as SpO_2 <80%, and bradycardia as heart rate <100/min. Duration of events was stratified ≥30 s, ≥60 s, and ≥120 s. SpO_2, oxygen saturation; $SctO_2$, cerebral tissue oxygen saturation; FiO_2, fraction of inspired oxygen; $tcpCO_2$, transcutaneous carbon dioxide pressure; h, hour. [a]Quantitative data are presented as mean ± SD using paired t test. [b]If Shapiro-Wilk normality test failed, median with 1st and 3rd quartile in brackets was calculated with Wilcoxon signed-rank test.

NIV modes have entered the clinical arena. Scientific data on their short-term advantages remain limited [17, 18]. Proponents of nHFOV argue that it provides more efficient pCO_2 elimination [10]. In this study, two widely used NIV modes were studied at equivalent respiratory settings for MAP and $tcCO_2$ to compare their efficacy in maintaining the SpO_2 within the target range. The results show clinically relevant variations in the primary outcome in an extent equivalent to the differences observed between manual and automated FiO_2 control [13, 19]. We did not observe significant differences in mean $SctO_2$ and below predefined limits which are in line with previous comparable studies where variations of SpO_2 within the target did not result in differences in $SctO_2$ measurements [13, 20, 21]. Although no impact on $SctO_2$ measurements was detected, the desaturations episodes are of major concern with respect to ROS production and their impact on the acute and long-term morbidities in preterm infants [1, 5]. The higher respiratory rates during sNIPPV need to be interpreted with caution as the recording was done by ECG-based impedance measurements and the sNIPPV mode with 40 mandatory breaths may have impacted the detected respiratory frequency. Otherwise, less respiratory effort and frequency might have been required during nHFOV to keep ventilation constant at the expense of higher FiO_2 requirements. Another explanation might be the suppression of the respiratory drive during nHFOV as previously observed in newborn lambs [22]. Abdominal distension, another concern associated with respiratory instability, did not differ between the groups. Our results support an intensified research focus on SpO_2 targeting to reduce the ROS burden which is driven not only by the constant exposure to oxygen but also by the fluctuations in SpO_2.

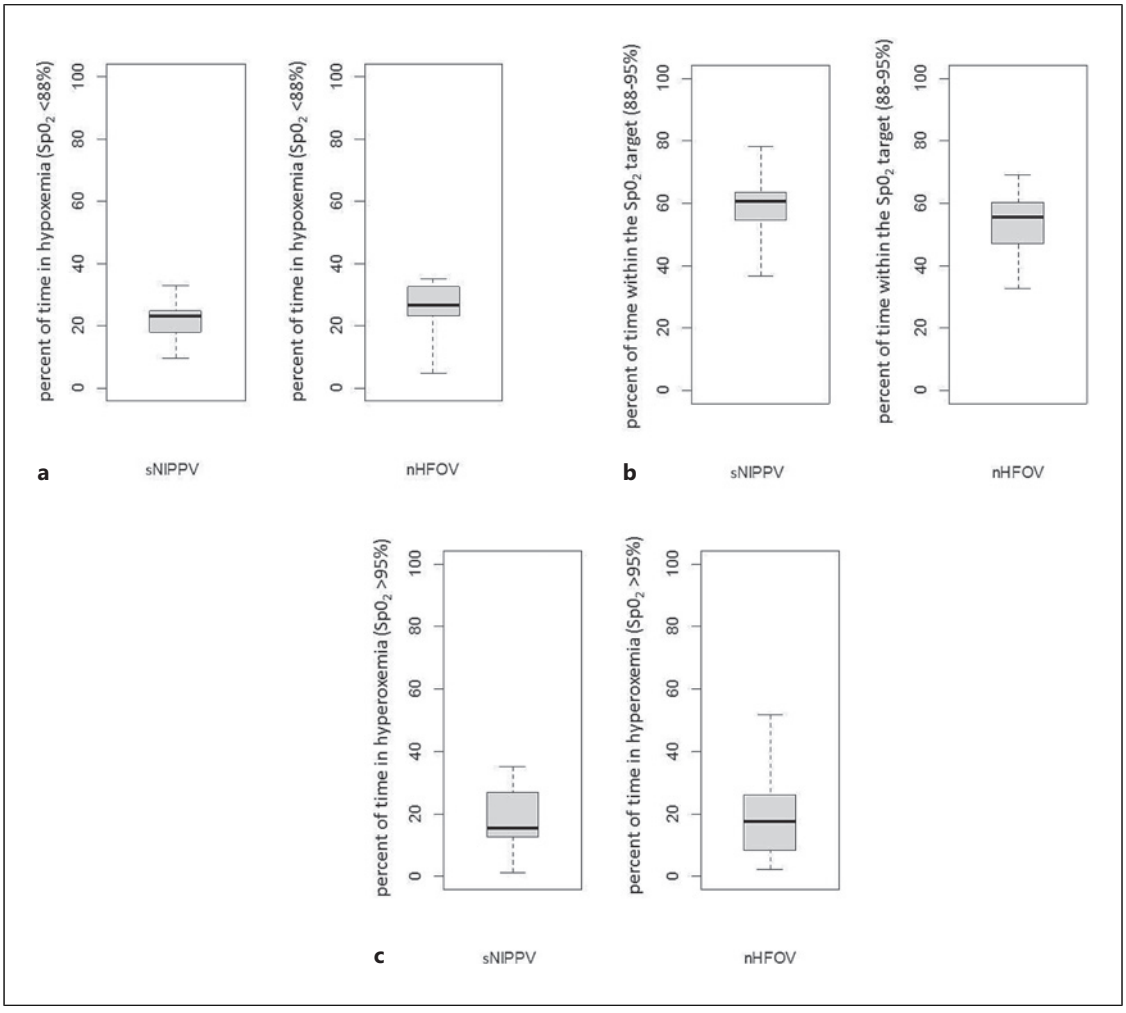

Fig. 2. Distribution of time spent in hypoxia, normoxia, and hyperoxia during sNIPPV and nHFOV. Depicted is the fraction of time spent in hypoxia (SpO_2 <88%, **a**), normoxia (SpO_2 88–95%, **b**), and hyperoxia (SpO_2 >95%, **c**) during sNIPPV and nHFOV presented as percentage of observation time of all $n = 22$ study patients during sNIPPV and nHFOV. SpO_2, oxygen saturation; sNIPPV, synchronized nasal intermittent positive pressure ventilation; nHFOV, nasal high-frequency oscillatory ventilation.

Strengths and Limitations of the Study

The major strength of our analysis is the comprehensive approach to multimodal signal recording of a magnitude of relevant patient parameters within a clinical routine setting. As SpO_2 targeting is particularly difficult in respiratory unstable infants on NIV, our data are of high clinical importance [13, 19]. As no other differences of such high relevance were observed when comparing these two NIV modes, sNIPPV should be the first priority in respiratory unstable infants when either sNIPPV or nHFOV is indicated.

Due to the limited duration of study intervals and the inclusion of patients with varying baseline characteristics, we are not able to specify the benefit to a precise gestational and postnatal age. But due to the strict inclusion criteria, pre-study respiratory parameters displayed a high inter-patient degree of correspondence within a patient population of very immature and respiratory unstable infants who have the highest risks for long-term morbidities. In line, the time spent within the SpO_2 target during sNIPPV with 59.9% was lower than in the majority of studies on this topic but within the expected range of comparable cohorts [23, 24]. This might have been overlooked in a more stable study population with less severe respiratory course. We need to acknowledge that an increase in mean airway pressure during nHFOV might have changed the outcome. Furthermore, the

translation of our results to non-synchronized NIPPV that is more widely available in neonatal intensive care units is not permitted [16, 17]. Another limitation is the decreased lower limit of the SpO_2 target compared to the recommended 91% that was used during clinical routine. This probably has aggravated the time spent in hypoxemia [19, 20]. We used a standardized protocol for FiO_2 titration that had been tested in such crossover settings before. However, it is not validated for reaction accuracy compared to FiO_2 adjustments exerted by experienced NICU staff based on the individual situation estimate that might have exaggerated the duration of time spent in hypoxemia [15]. Furthermore, adherence to the protocol was not monitored. On the other hand, the averaging time of 8 s of the used SpO_2 monitor might have led to an underestimation of SpO_2 fluctuations. Lastly, we did not detect an effect on $SctO_2$. Compensation mechanisms for maintaining cerebral oxygenation in situations of impaired SpO_2 can explain this disparity [13, 21, 25]. Nonetheless, the data from the Canadian oxygen trial argue toward a relevant impact of prolonged fluctuations in SpO_2 [4, 6].

Conclusion

Implications for Clinical Practice and Future Research Directions

Even more than 50 years after the first description of NIV in preterm infants, the evidence for superiority of one mode over the other remains limited [6, 16]. The results from the large oxygen targeting trials highlighted this scientific need [26]. The NICU was littered with a variety of novel NIV modes during the recent decade and their implementation was based on theoretical considerations and best individual outcome measures. SpO_2 targeting during nHFOV was not in the focus of research. The presented data disclose its inferiority in that aspect compared to sNIPPV. In more general terms, our results underpin the need and opportunity to put research priorities on the optimal mode of NIV to retain oxygen targeting.

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Statement of Ethics

The study was reviewed and approved by the Local Ethics Committee of the medical faculty of the Justus-Liebig-University Giessen (Az 149/19) and was executed according to the Declaration of Helsinki. The study was registered at the German Clinical Trials Register (DRKS00023438, https://drks.de/search/en/trial/DRKS00023438). Written parental informed consent was acquired prior to study inclusion. Patients were recruited between September 2020 and October 2021.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Svilen Atanasov: conceptualization (supporting); data acquisition (lead); data analysis; and revising the article for important intellectual content (supporting). Constanze Dippel and Rahel Schuler: data acquisition (supporting); data analysis; and revising the article for important intellectual content (supporting). Dupleix Takoulegha: development data acquisition tool (lead) and writing and revising the article for important intellectual content (supporting). Anita Windhorst, Inez Frerichs, and Claas Strodthoff: data analysis and revising the article for important intellectual content (supporting). Jens Dreyhaupt: data analysis (lead); revising the article for important intellectual content (supporting). Markus Waitz: conceptualization (supporting); writing manuscript; and revising the article for important intellectual content (supporting). Keywan Sohrabi: conceptualization (lead); development data acquisition tool (lead); and writing and revising the article for important intellectual content (supporting). Harald Ehrhardt: conceptualization (lead); writing manuscript and revising the article for important intellectual content (lead). All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

Deidentified individual participant data including data dictionaries will be made available upon publication to researchers who provide a reasonable and methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to the corresponding author.

References

1 Choi Y, Rekers L, Dong Y, Holzfurtner L, Goetz MJ, Shahzad T, et al. Oxygen toxicity to the immature lung: part I–pathomechanistic understanding and preclinical perspectives. Int J Mol Sci. 2021;22(20):11006.
2 Di Fiore JM, Vento M. Intermittent hypoxemia and oxidative stress in preterm infants. Respir Physiol Neurobiol. 2019;266:121–9.
3 Di Fiore JM, Kaffashi F, Loparo K, Sattar A, Schluchter M, Foglyano R, et al. The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants. Pediatr Res. 2012;72(6):606–12.
4 Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA. 2015;314(6):595–603.
5 Behnke J, Dippel CM, Choi Y, Rekers L, Schmidt A, Lauer T, et al. Oxygen toxicity to the immature lung: part II–the unmet clinical need for causal therapy. Int J Mol Sci. 2021;22(19):10694.
6 Jensen EA, Whyte RK, Schmidt B, Bassler D, Vain NE, Roberts RS, et al. Association between intermittent hypoxemia and severe bronchopulmonary dysplasia in preterm infants. Am J Respir Crit Care Med. 2021;204(10):1192–9.
7 Reyburn B, Di Fiore JM, Raffay T, Martin RJ, Prakash YS, Jafri A, et al. The effect of continuous positive airway pressure in a mouse model of hyperoxic neonatal lung injury. Neonatology. 2016;109(1):6–13.
8 Behnke J, Lemyre B, Czernik C, Zimmer KP, Ehrhardt H, Waitz M. Non-invasive ventilation in neonatology. Dtsch Arztebl Int. 2019;116(11):177–83.
9 Dumpa V, Bhandari V. Non-invasive ventilatory strategies to decrease bronchopulmonary dysplasia: where are we in 2021. Children. 2021;8(2):132.
10 Li J, Chen L, Shi Y. Nasal high-frequency oscillatory ventilation versus nasal continuous positive airway pressure as primary respiratory support strategies for respiratory distress syndrome in preterm infants: a systematic review and meta-analysis. Eur J Pediatr. 2022;181(1):215–223.
11 Seth S, Saha B, Saha AK, Mukherjee S, Hazra A. Nasal HFOV versus nasal IPPV as a post-extubation respiratory support in preterm infants-a randomised controlled trial. Eur J Pediatr. 2021;180(10):3151–60.
12 Waitz M, Mense L, Kirpalani H, Lemyre B. Nasal intermittent positive pressure ventilation for preterm neonates: synchronized or not? Clin Perinatol. 2016;43(4):799–816.
13 Waitz M, Schmid MB, Fuchs H, Mendler MR, Dreyhaupt J, Hummler HD. Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations. J Pediatr. 2015;166(2):240–4.e1.
14 Lauer T, Behnke J, Oehmke F, Baecker J, Gentil K, Chakraborty T, et al. Bacterial colonization within the first 6 weeks of life and pulmonary outcome in preterm infants <1,000 g. J Clin Med. 2020;9(7):2240.
15 Sink DW, Hope SAE, Hagadorn JI. Nurse: patient ratio and achievement of oxygen saturation goals in premature infants. Arch Dis Child Fetal Neonatal Ed. 2011;96(2):F93–8.
16 Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev. 2016;12(12):CD005384.
17 Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2017;2(2):CD003212.
18 Zhu X, Feng Z, Liu C, Shi L, Shi Y, Ramanathan R, et al. Nasal high-frequency oscillatory ventilation in preterm infants with moderate respiratory distress syndrome: a multicenter randomized clinical trial. Neonatology. 2021;118(3):325–31.
19 van Kaam AH, Hummler HD, Wilinska M, Swietlinski J, Lal MK, te Pas AB, et al. Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. J Pediatr. 2015;167(3):545–50.e1–2.
20 Schmid MB, Hopfner RJ, Lenhof S, Hummler HD, Fuchs H. Cerebral desaturations in preterm infants: a crossover trial on influence of oxygen saturation target range. Arch Dis Child Fetal Neonatal Ed. 2013;98(5):F392–8.
21 Dani C, Pratesi S, Luzzati M, Petrolini C, Montano S, Remaschi G, et al. Cerebral and splanchnic oxygenation during automated control of inspired oxygen (FiO_2) in preterm infants. Pediatr Pulmonol. 2021;56(7):2067–72.
22 Hadj-Ahmed MA, Samson N, Nadeau C, Boudaa N, Praud JP. Laryngeal muscle activity during nasal high-frequency oscillatory ventilation in nonsedated newborn lambs. Neonatology. 2015;107(3):199–205.
23 Dargaville PA, Marshall AP, Ladlow OJ, Bannink C, Jayakar R, Eastwood-Sutherland C, et al. Automated control of oxygen titration in preterm infants on non-invasive respiratory support. Arch Dis Child Fetal Neonatal Ed. 2022;107(1):39–44.
24 Ali SK, Jayakar RV, Marshall AP, Gale TJ, Dargaville PA. Preliminary study of automated oxygen titration at birth for preterm infants. Arch Dis Child Fetal Neonatal Ed. 2022;107(5):539–44.
25 Mayer B, Pohl M, Hummler HD, Schmid MB. Cerebral oxygenation and desaturations in preterm infants: a longitudinal data analysis. J Neonatal Perinatal Med. 2017;10(3):267–73.
26 Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, et al. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. JAMA. 2018;319(21):2190–201.