# Carbon Dioxide Level between Nasal High-Frequency Oscillatory Ventilation and Synchronized Nasal Intermittent Positive Pressure Ventilation after Extubation in Neonates: A Cross-over Randomized Controlled Trial

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## Abstract

**Objective** Nasal high-frequency oscillatory ventilation (nHFOV) and synchronized nasal intermittent positive pressure ventilation (sNIPPV) yield a lower partial pressure of carbon dioxide ($pCO_2$) after extubation than nasal continuous positive airway pressure. Our aim was to clarify which of the two was superior.

**Study Design** We performed a crossover randomized study to evaluate $pCO_2$ level among 102 participants from July 2020 to June 2022. Intubated preterm and term neonates with arterial lines were randomly allocated to nHFOV–sNIPPV or sNIPPV–nHFOV sequences; their $pCO_2$ levels were measured after 2 hours in each mode. Subgroup analyses were performed for preterm (gestational age <37 weeks) and very preterm (gestational age <32 weeks) neonates.

**Results** The mean gestational age (nHFOV–sNIPPV, 32.8 vs. sNIPPV–nHFOV, 33.5 weeks) and median birth weight (1,850 vs. 1,930 g) did not differ between the sequences. The mean ± standard deviation $pCO_2$ level after nHFOV (38.7 ± 8.8 mm Hg) was significantly higher than that after sNIPPV (36.8 ± 10.2 mm Hg; mean difference: 1.9 mm Hg; 95% confidence interval: 0.3–3.4 mm Hg; treatment effect [$p = 0.007$] but no sequence [$p = 0.92$], period [$p = 0.53$], or carryover [$p = 0.94$] effects). However, the difference in $pCO_2$ level between the sequences was not statistically significant in the subgroup analyses of preterm and very preterm neonates.

**Conclusion** After neonatal extubation, the sNIPPV mode was associated with a lower $pCO_2$ level than the nHFOV mode with no significant difference in preterm and very preterm neonates.

**Keywords**
- airway extubation
- carbon dioxide
- high-frequency ventilation
- intermittent positive pressure ventilation
- newborn
- noninvasive ventilation

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## Key Points

- Full noninvasive ventilation support is suggested in neonatal ventilation.
- $pCO_2$ level in sNIPPV was lower than in nHFOV.
- No differences in $pCO_2$ levels were observed in either preterm or very preterm neonates.

Noninvasive ventilation (NIV) is used as a primary or postextubation mode of respiratory support to reduce pulmonary complications from intubation and prolonged invasive mechanical ventilation.[1–3] Nasal continuous positive airway pressure (nCPAP) has been applied as a standard mode of NIV for several decades. However, in the past decade, synchronized nasal intermittent positive pressure ventilation (sNIPPV) and nasal high-frequency oscillatory ventilation (nHFOV) have been increasingly utilized in neonatal medicine.[4] sNIPPV is used to deliver synchronized intermittent positive pressure during the inspiratory phase[5] and nHFOV is used to generate oscillation without synchrony over continuous positive airway pressure.[6]

In a meta-analysis, sNIPPV (9.4% [17/180]) was shown to more efficacious than nCPAP (39.5% [68/172]) in preventing postextubation failure.[7] From three randomized controlled trials (RCTs), the partial pressure of carbon dioxide ($pCO_2$) level during sNIPPV was lower than that during nCPAP in postextubation.[8–10] Mean ± standard deviation (SD) $pCO_2$ levels after sNIPPV versus nCPAP were $37 \pm 1$ versus $40 \pm 2$,[9] $42.9 \pm 2.2$ versus $44.8 \pm 2.2$,[10] and $50 \pm 9$ versus $53 \pm 9$[8] mm Hg. In a recent review and meta-analysis, nHFOV was superior to single-level and biphasic nCPAP in preventing reintubation (odds ratio: 0.3; $p < 0.001$) and potentially in reducing $pCO_2$ levels (mean difference: −4.6 mm Hg; $p = 0.05$).[6]

In previous meta-analyses, the mean airway pressure (MAP) in NIPPV[7] and nHFOV[11] was similar or higher than that in nCPAP. In an RCT, the rate of extubation failure in preterm infants was lower with an nCPAP range of 7 to 9 cm $H_2O$ than that with a range of 4 to 6 cm $H_2O$.[12] Thus, the mechanisms of any apparent advantages of sNIPPV and nHFOV, except for the higher MAP, are unclear. There is paucity of literature from RCTs comparing nHFOV with sNIPPV. Henceforth, this crossover RCT aimed to compare the 2-hour $pCO_2$ level between nHFOV and sNIPPV after extubation.

## Materials and Methods

### Setting and Participants

We performed an open-label and crossover RCT in a university-based tertiary referral neonatal intensive care unit in Southern Thailand from July 2020 to June 2022. This RCT was approved by the Human Research Ethics Committee of our institution (approval no.: REC. 62-382-1-1) and registered on *ClinicalTrials.gov* (NCT04323397).

All inborn preterm and term neonates who were admitted to the neonatal intensive care unit, had undergone their first endotracheal intubation, and needed NIV after extubation were assessed for eligibility. We excluded neonates with (1) no arterial catheterization; (2) major congenital anomalies or chromosomal abnormalities; (3) neuromuscular diseases; (4) upper respiratory tract abnormalities; (5) congenital lung diseases or pulmonary hypoplasia; (6) surgical conditions known before the first extubation; (7) grade IV intraventricular hemorrhage occurring before the first extubation; (8) palliative care; or (9) the parents' decision not to participate. Withdrawal criteria were (1) reintubation during the crossover period and (2) the parents' decision for their neonate not to continue participation.

### Randomization

Stratification was performed based on gestational age (GA) (< or ≥32 weeks), oxygenation index (OI) (< or ≥12), and intubation period (< or ≥7 days). Participants were randomly allocated (1:1) to one of two treatment sequences (nHFOV–sNIPPV or sNIPPV–nHFOV) in the crossover design (►Fig. 1; ►Supplementary Table S1, available in the online version). The allocation sequence was performed via computer generation permuted-block randomization and sealed-envelope allocation were used. Caregivers were not blinded to the intervention owing to its nature.

### Procedure

Intravenous aminophylline was routinely prescribed after birth or ≥24 hours before extubation for preterm neonates with a birth weight (BW) <1,250 g. The mode of invasive ventilation was chosen as deemed appropriate by the attending staff; however, HFOV was used as the primary therapy in most intubated cases until extubation. Chest X-rays and arterial blood gas (ABG) testing were generally performed before extubation. At the time of the study, no consensus recommendations for extubation criteria or initial and discontinuation NIV settings were available. Therefore, the attending neonatologists followed institutional guidelines. Extubation criteria were as follows: the ventilated neonate had an oxygen saturation >90%, a fraction of inspired oxygen <0.4, and acceptable ABG test results (pH >7.25, $pCO_2$ <60 mm Hg), with the respiratory settings detailed in ►Table 1. Informed consent was obtained from parents by neonatal fellows. After patient enrollment, group allocation was immediately performed by the same neonatal fellows.

The initial NIV settings in the crossover phase are described in ►Table 1. ABG testing was performed 2-hour postintervention. It was performed again 2 hours after switching the mode of NIV, without a washout period. Both modes of NIV were provided with the SLE6000 infant ventilator (SLE, London, United Kingdom) via a nasal mask. Although our unit also had access to other ventilators, only the SLE6000 ventilator could be set to either nHFOV or sNIPPV. In all cases in which the nSIPPV mode was used, a pressure trigger system was used to provide synchronization

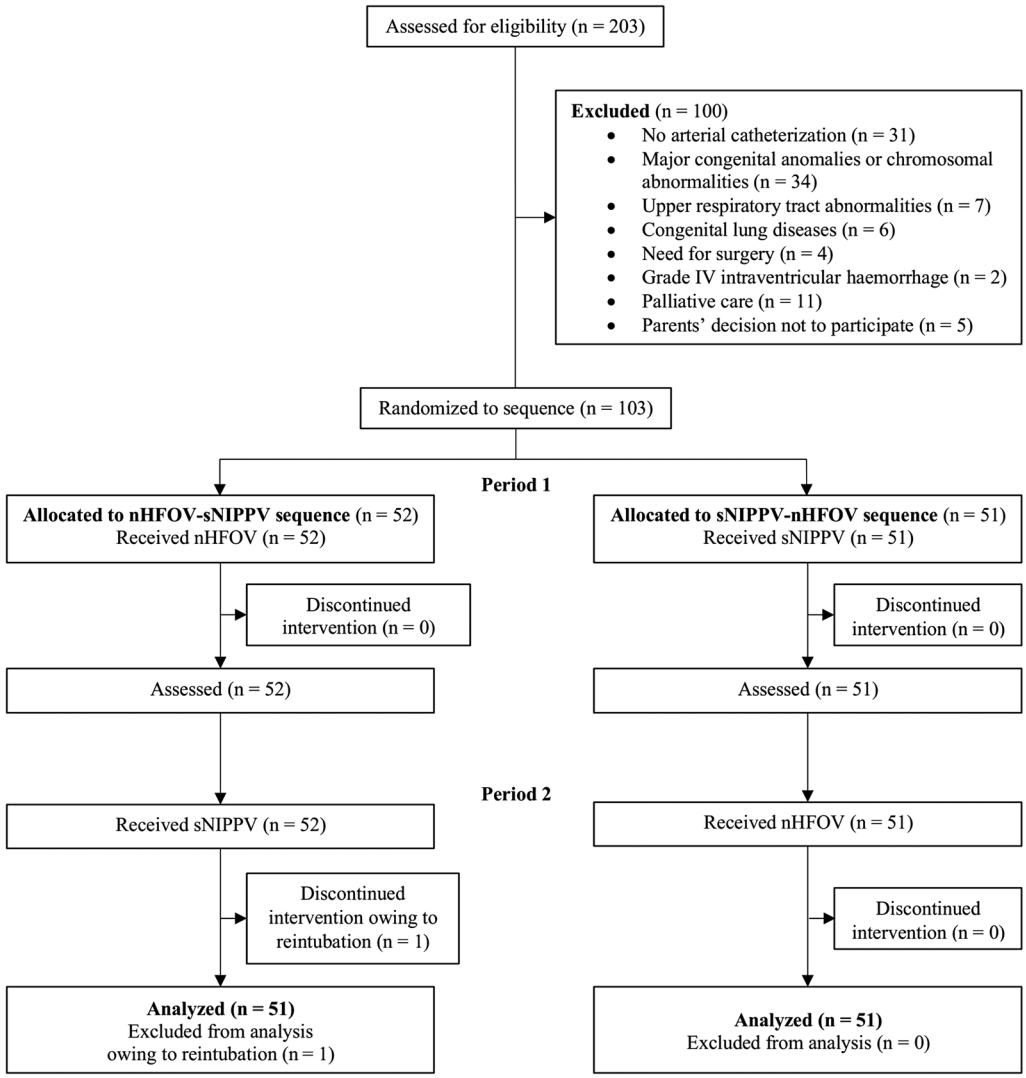


**Fig. 1** Consolidated Standards of Reporting Trials diagram of participants. A diagram showing patients allocated to the nasal high-frequency oscillatory ventilation (nHFOV) or synchronized nasal intermittent positive pressure ventilation (sNIPPV) groups.

**Table 1** Extubation criteria for high-frequency oscillatory ventilation, synchronized intermittent positive pressure ventilation, and initial protocol settings of nasal high-frequency oscillatory ventilation and nasal synchronized intermittent positive pressure ventilation

| Invasive mode | HFOV | SIPPV |
|---|---|---|
| Extubation criteria | Flow = 6–10 L/min, frequency = 10 Hz, MAP = 6–7 cm $H_2O$ for preterm or 7–9 cm $H_2O$ for term neonates, amplitude = 12–20 cm $H_2O$, I:E = 1:1 | Flow = 6–10 L/min, rate = 30 breaths/min, PIP = 12–15 cm $H_2O$, PEEP = 3 cm $H_2O$ |
| Noninvasive mode | Nasal HFOV | Nasal SIPPV |
| Initial noninvasive settings | Flow = 8–10 L/min, frequency = 10 Hz, MAP = "MAP (before extubation) + 2" or 8 (preterm)/10 (term) cm $H_2O$, amplitude = 2–3 times that of MAP with visible chest oscillatory ventilations or 25–35 cm $H_2O$, I:E = 1:1, $FiO_2$ = "$FiO_2$ (before extubation) + 0.1–0.2" while keeping targeted $SpO_2$ 90–94% | Flow = 8–10 L/min, rate = 40–60 breaths/min, PIP = "PIP (before extubation) + 2–5" or 20 (preterm)/25 (term) cm $H_2O$, PEEP = 5 cm $H_2O$, Ti = 0.4–0.5 s $FiO_2$ = "$FiO_2$ (before extubation) + 0.1–0.2" while keeping targeted $SpO_2$ 90–94%. The highest trigger sensitivity avoiding auto triggering was selected |

Abbreviations: $FiO_2$, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; I:E, inspiratory:expiratory; MAP, mean airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; SIPPV, synchronized intermittent positive pressure ventilation; $SpO_2$, oxygen saturation; Ti, inspiratory time.

in the sNIPPV mode. We applied a pacifier (Jollypop; Sandbox Medical, Pembroke, MA) to soothe preterm and term neonates and minimize oral leakage. A disposable ventilator circuit (Fisher & Paykel RT268, Evaqua Dual Limb Infant Breathing Circuit Kit with Evaqua 2 Technology and Pressure Line; Fisher & Paykel, Auckland, New Zealand) was used.

Arterial $pCO_2$ was measured via ABG testing. Approximately 1 mL of arterial blood was drawn with a nonheparinized syringe, and 0.2 mL was separately obtained with a heparinized polyethylene syringe. All blood samples were analyzed using the ABL800 BASIC blood gas and electrolytes analyzer (Radiometer Medical ApS; Radiometer, Copenhagen, Denmark) within 1 minute of blood collection.

Criteria for reintubation were as follows: (1) cardiorespiratory arrest or any type of pulmonary hemorrhage; (2) persistent low blood pressure with no response to volume expanders and vasoactive agents; (3) stupor or persistent drowsiness after initial correction and care; (4) severe respiratory distress, e.g., persistent cyanosis, marked retraction, and nasal flaring, unresponsive to oxygen supplementation; (5) 2 hours of respiratory acidosis with $pCO_2$ >70 mm Hg and pH <7.2; (6) 2 hours of hypoxia with a partial pressure of oxygen <50 mm Hg and a fraction of inspired oxygen >0.6; (7) apnea occurring ≥3 times/h and a heart rate <100 beats/min, or apnea necessitating bag-and-mask ventilation; and (8) severe postextubation stridor.

### Outcomes

The primary outcome was the arterial $pCO_2$ level after 2 hours of nHFOV compared with that after 2 hours of sNIPPV. Subgroup analyses were performed for preterm (GA <37 weeks) and very preterm (GA <32 weeks) neonates.

### Sample Size

From previous studies in which nHFOV or sNIPPV were compared with nCPAP in very low BW infants, the mean ± SD $pCO_2$ level yielded by nHFOV and sNIPPV was 35.1 ± 7.8[13] and 50 ± 9[8] mm Hg, respectively. Using a significance level of <5% with 80% power, a sample of 12 very preterm neonates was required for the detection of a difference of $pCO_2$ level between the two modes. Approximately 50 neonates who were intubated in our unit were included per year, of whom very preterm neonates comprised 30 to 40%. We performed a 2-year study (50–60 participants [15–20 very preterm neonates] per arm) to increase the power of the study and recruit sufficient very preterm neonates.

### Statistical Analysis

R software (version 4.0.3; The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical comparisons. STATA software (version 17, StataCorp LLC, College Station, TX) was used to analyze the treatment, sequence, period, and carryover effects, with $p$ <0.05 deemed statistically significant. Categorical variables were presented as percentages and compared using the $\chi^2$ or Fisher's exact test. The Shapiro–Wilk test was used to determine the normality of continuous variables. Parametric variables were presented as means ± SDs and compared using Student's $t$-test. Nonparametric variables were presented as medians (interquartile ranges) and compared using the Wilcoxon's rank-sum test.

## Results

Overall, 203 neonates were assessed for eligibility and 100 neonates were excluded (►Fig. 1). Finally, 103 neonates were randomly allocated to the study sequences (nHFOV–sNIPPV = 52, sNIPPV–nHFOV = 51). Owing to one extubation failure (nHFOV–sNIPPV group due to persistent drowsiness at 3.5 hours after extubation) during the crossover period, 102 neonates were included for final analysis. The median GA and BW were 33 (30–37) weeks and 1,920 (1,364–2,887) g, respectively. The numbers of term, preterm, and very preterm neonates in the nHFOV–sNIPPV group were 10, 41, and 19, respectively; those in the sNIPPV–nHFOV group were 17, 34, and 20, respectively. The median duration of invasive mechanical ventilation was 45.8 (21.1–87.5) hours. Baseline characteristics and those before extubation in the nHFOV–sNIPPV and sNIPPV–nHFOV groups are shown in ►Table 2.

NIV settings after extubation are summarized in ►Table 3. The median MAP with sNIPPV was higher than that with nHFOV, but no significant difference (9 [9–9] vs. 11 [8–12.5] cm $H_2O$, $p = 0.06$) was observed. The individual $pCO_2$ levels after 2 hours of NIV in each treatment sequence are illustrated in ►Fig. 2. The final ABG samples after sNIPPV and nHFOV were 102 and 102 samples, respectively. The number of $pCO_2$ <25 mm Hg events after sNIPPV (12 events in 102 samples) was similar to that after nHFOV (10 events in 102 samples). The pH ranges in these neonates were 7.449 to 7.663 and 7.373 to 7.505 with sNIPPV and nHFOV, respectively. However, in two instances, the $pCO_2$ level dropped to approximately 10 mm Hg (pH: 7.650–7.663), both events occurring after sNIPPV (►Fig. 2). The only instance of the $pCO_2$ level rising above 60 mm Hg (pH: 7.171) also occurred after sNIPPV.

Between the two NIV modes, the mean $pCO_2$ level after 2 hours of nHFOV and sNIPPV was 38.7 ± 8.8 and 36.8 ± 10.2 mm Hg. The $pCO_2$ levels after 2 hours of nHFOV were significantly higher than those after sNIPPV (mean difference [95% confidence interval] of 1.9 [0.3–3.4] mm Hg; treatment effect [$p = 0.007$], but no sequence [$p = 0.92$], period [$p = 0.53$], or carryover [$p = 0.94$] effects). However, the difference was not statistically significant in the subgroup analyses of preterm and very preterm neonates (►Table 4).

## Discussion

The $pCO_2$ level was reported in three RCTs on sNIPPV.[8–10] In those studies, the mean GA and BW of participants were 26 to 28 weeks and 800 to 1,000 g, respectively. The ventilators used were the InfantStar ventilator with the pneumatic StarSync capsule[9,10] and the Stephanie ventilator and the VIP Bird ventilator.[8] The settings for the sNIPPV mode varied among the studies, including the respiratory rate (RR; 10[10] and 15–25[9] breaths/min), peak inspiratory pressure (PIP;

 

**Table 2** Baseline characteristics and those before extubation of participants in both modes

| | nHFOV–sNIPPV ($n = 51$) | sNIPPV–nHFOV ($n = 51$) |
|---|---|---|
| Baseline characteristics | | |
| Gestational age, wk[a] | 32.8 ± 4 | 33.5 ± 4 |
| Birth weight, g[b] | 1,850 (1,335–2,772) | 1,930 (1,395–2,898) |
| Small for gestational age | 5 (10) | 6 (12) |
| Male | 36 (71) | 23 (45) |
| Cesarean delivery | 41 (80) | 41 (80) |
| 5-min Apgar score[b] | 9 (8–9) | 8 (8–9) |
| Indication for intubation | | |
| Respiratory distress syndrome | 29 (57) | 27 (53) |
| Transient tachypnea of the newborn | 11 (22) | 14 (27) |
| Meconium aspiration syndrome | 5 (10) | 7 (14) |
| Persistent pulmonary hypertension | 3 (6) | 1 (2) |
| Birth asphyxia | 2 (4) | 1 (2) |
| Others | 1 (2) | 1 (2) |
| Prophylactic methylxanthines | 17 (33) | 17 (33) |
| Before extubation | | |
| High-frequency oscillatory ventilation | 42 (82) | 45 (88) |
| Mean airway pressure, cm $H_2O$[b] | 7 (7–8) | 7 (7–8) |
| Oxygenation index[b] | 2.5 (2.0–3.3) | 2.6 (2.0–3.5) |
| Postnatal age, h[b] | 69.2 (22.6–102.8) | 47.6 (16.8–77.2) |
| Body weight, g[b] | 1,720 (1,315–2,763) | 2,058 (1,434–2,958) |
| Duration of intubation, h[b] | 63.4 (21.5–91.7) | 38.8 (15.7–73.5) |

Abbreviations: nHFOV, nasal high-frequency oscillatory ventilation; sNIPPV, synchronized nasal intermittent positive pressure ventilation.
Note: Data are presented as no. (%) unless otherwise indicated.
[a]Mean ± standard deviation.
[b]Median (interquartile range).

10–20,[8] 13–23[10] cm $H_2O$, and the PIP from the prior invasive mode plus 2–4 cm $H_2O$[9]). The interfaces were nasal prongs in all those studies.[8–10] Mean $pCO_2$ levels from previous studies were 37 ± 1,[9] 42.9 ± 2.2,[10] and 50 ± 9[8] mm Hg. In this study, the mean GA and BW were 33 weeks and 1,920 g, respectively, both higher than those in the studies mentioned above. The RR and PIP were set to 60 breaths/min and 20 to 25 cm $H_2O$ (both higher than those in previous studies), respectively, via a nasal mask. The mean $pCO_2$ level was 36.8 ± 10.2 mm Hg. Overall, 2 $pCO_2 \approx 10$ mm Hg events and 21 $pCO_2 < 30$ mm Hg events were observed, which might have resulted from the higher RR and PIP in this study than those in most previous studies. Only one participant had a $pCO_2 > 60$ mm Hg event. In one RCT, the $pCO_2$ level ranged from 18 to 61 mm Hg.[10]

The $pCO_2$ level was reported in two recent RCTs,[14,15] respectively, in which nHFOV was compared with non-synchronized NIPPV. The GA was less than 34[15] and 37[14]

**Table 3** Nasal high-frequency oscillatory ventilation and synchronized nasal intermittent positive pressure ventilation settings

| | nHFOV (102 periods) | sNIPPV (102 periods) |
|---|---|---|
| Frequency | 10 Hz | 60 breaths/min |
| Mean airway pressure, cm $H_2O$, median (interquartile range) | 9 (9–9) | 11 (8–12.5) |
| Pressure, cm $H_2O$ | Delta pressure | PIP/PEEP |
| | 20 cm $H_2O$ = 15 periods | 20/5 cm $H_2O$ = 64 periods |
| | 25 cm $H_2O$ = 68 periods | 25/5 cm $H_2O$ = 38 periods |
| | 30 cm $H_2O$ = 17 periods | |
| | 35 cm $H_2O$ = 2 periods | |

Abbreviations: nHFOV, nasal high-frequency oscillatory ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; sNIPPV, synchronized nasal intermittent positive pressure ventilation.

 

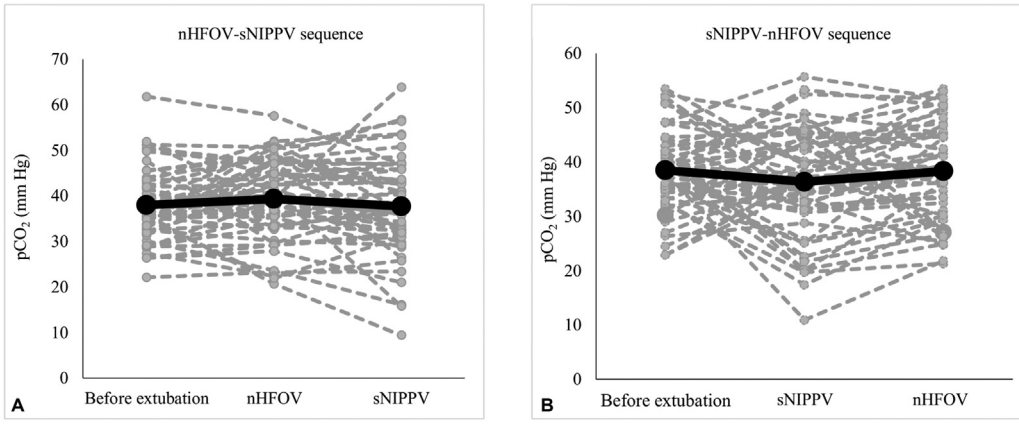


**Fig. 2** The individual partial pressure of carbon dioxide ($pCO_2$) after 2 hours of noninvasive ventilation of each neonate randomly allocated to the (**A**) nasal high-frequency oscillatory ventilation (nHFOV)-synchronized nasal intermittent positive pressure ventilation (sNIPPV) and (**B**) sNIPPV–nHFOV sequence groups.

weeks in those studies. The brands of ventilator used for nHFOV were SLE[14] and Fabian high-frequency oscillation.[15] The settings (ranges) for the nHFOV mode varied between studies, including the frequency, 10 (6–15) Hz; MAP, 8–10 (5–16) cm $H_2O$; and amplitude, 25 (25–50) cm $H_2O$.[14,15] The interfaces were either only nasal prongs[15] or cycled between prongs and masks.[14] In one RCT on preterm infants,[14] median $pCO_2$ levels before and after nHFOV were 41.3 (32.0–47.4) and 33.8 (29.1–41.0) mm Hg, respectively. In another RCT on very low BW infants,[15] mean $pCO_2$ levels before and after nHFOV were $41.47 \pm 3.79$ and $41.58 \pm 3.65$ mm Hg, respectively. In this study, the settings for nHFOV were as follows: frequency = 10 Hz, MAP = 9 (9–10) cm $H_2O$, amplitude = 25 (20–35) cm $H_2O$, and inspiratory time = 50%, similar to those in previous studies. The mean $pCO_2$ level after nHFOV was $38.7 \pm 8.8$ mm Hg.

In meta-analyses, nHFOV removed significantly more $pCO_2$ than nCPAP.[6,11] Both nHFOV and sNIPPV are reportedly superior to nCPAP in preventing extubation failure.[6,7] In a network meta-analysis, sNIPPV (surface under the cumulative ranking curve = 0.97) and nHFOV (surface under the cumulative ranking curve = 0.82) yielded significantly lower reintubation rates than nCPAP.[16] In a recent meta-analysis, nHFOV resulted in a lower reintubation rate in preterm infants (risk ratio = 0.72) than nonsynchronized NIPPV.[17] Therefore, both $pCO_2$ clearance and extubation success are still inconclusive as to which of the two modes are the most beneficial. Differences in patient characteristics, ventilator settings, type of ventilator or ventilator circuit, method of synchronization in sNIPPV, type of nasal interface, and nursing care might have resulted in the different outcomes in our and previous studies.[5,6,18–20] The experience of clinicians and nurses in NIV use and nasal interface caring is of particular importance. Therefore, further investigation is required into both physiological and clinical outcomes.

This study's strengths included its internal and external validities. This trial filled a knowledge gap in comparing the efficacies of the nHFOV and sNIPPV modalities in $CO_2$ clearance. The crossover design enabled minimization of confounding effects and maximization of the power of the study. The first mode of NIV was randomized to minimize selection bias. Enrolled participants comprised both term and preterm neonates, and subgroup analyses of these were separately compared with results of previous studies. Therefore, the results are applicable to clinical practice for neonates with a wide range of GAs.

The major limitations of the present study are as follows. First, we included only extubated neonates who needed NIV, which was subjectively determined by attending staff. We have not had an indication or criterion for NIV both term and preterm neonates after extubation. Second, enrolled participants all had mild respiratory conditions before extubation (average OI = 2.5, ventilator days = 2–3 days, duration of NIV = 1 day duration of oxygen use after extubation = 4 days), whereas the mean OI in neonates receiving nHFOV before extubation in previous studies was $3.8 \pm 2.7$[21] and $4.5 \pm 0.4$.[15] Hence, this study might have included term neonates who had respiratory conditions of lower severity than those in previous studies. Third, no standardized protocol existed for either NIV mode at the time of the study. The $pCO_2$ level during sNIPPV was lower than that during nHFOV, which has multiple possible explanations. The RR during sNIPPV, 60 breaths/min in the crossover study, was higher than that in other studies (range, 15–50 breaths/min).[8,9,22–26] The MAP yielded by sNIPPV was higher than that yielded by nHFOV. During NIV, the flow sensor was turned off and respiratory function was not monitored (e.g., spontaneous RR and minute ventilation). Fourth, the triggering device for sNIPPV in this study was pressure. The disadvantages of a pressure trigger for sNIPPV is its low sensitivity, causing frequent autotriggering or no triggering; autotriggering caused by secretions or leaks; and the lack of flow monitoring.[5] Fifth, no washout period was implemented during the crossover intervention; however, an optimal time (2 hours) was allowed for each intervention before measurements were made. ABG testing could mostly be performed 30 minutes after adjustment of the invasive ventilatory settings. In previous studies, ABG testing was performed 1 to 2,[27] 1 to 3,[8,9] 4,[28] 6,[29] and 12-hour[14] post-NIV. Sixth, although the $pCO_2$ levels during sNIPPV were lower

 

**Table 4** Primary outcome of partial pressure of carbon dioxide, partial pressure of carbon dioxide level and subgroup analyses for preterm and very preterm neonates following nasal high-frequency oscillatory ventilation–synchronized nasal intermittent positive pressure ventilation versus synchronized nasal intermittent positive pressure ventilation–nasal high-frequency oscillatory ventilation sequences

| Sequence | nHFOV–sNIPPV | | | sNIPPV–nHFOV | | | *p*-Value | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Mode of respiratory support | Before extubation | nHFOV | sNIPPV | Before extubation | sNIPPV | nHFOV | Treatment effect[a] | Carryover effect[b] | Sequence effect[a] | Period effect[a] |
| All cases | ($n=51$) | | | ($n=51$) | | | *p*-Value | | | |
| $pCO_2$ level | 38.0 ± 7.9 | 39.3 ± 8.9 | 37.7 ± 10.8 | 38.4 ± 7.6 | 35.9 ± 9.6 | 38.0 ± 8.8 | 0.02 | 0.23 | 0.35 | 0.76 |
| $pCO_2$ difference | NA | 1.4 ± 7.8 | −1.6 ± 8.1 | NA | −2.6 ± 10.6 | 2.1 ± 8.0 | 0.007 | 0.94 | 0.92 | 0.53 |
| Only preterm | ($n=41$) | | | ($n=34$) | | | *p*-Value | | | |
| $pCO_2$ level | 37.1 ± 7.4 | 39.2 ± 9.3 | 38.2 ± 11.2 | 37.3 ± 7.8 | 36.3 ± 10.2 | 37.9 ± 9.6 | 0.17 | 0.34 | 0.46 | 0.73 |
| $pCO_2$ difference | NA | 2.0 ± 7.9 | −0.9 ± 8.3 | NA | −1.0 ± 10.9 | 1.7 ± 8.2 | 0.10 | 0.87 | 0.84 | 0.94 |
| Only very preterm | ($n=19$) | | | ($n=20$) | | | *p*-Value | | | |
| $pCO_2$ level | 35.9 ± 6.6 | 37.9 ± 10.0 | 36.7 ± 11.9 | 37.7 ± 9.6 | 38.5 ± 9.0 | 39.5 ± 9.9 | 0.37 | 0.47 | 0.58 | 0.93 |
| $pCO_2$ difference | NA | 2.1 ± 7.5 | −1.2 ± 6.3 | NA | 0.8 ± 10.1 | 1.0 ± 8.6 | 0.40 | 0.80 | 0.79 | 0.46 |

Abbreviations: NA, not applicable; nHFOV, nasal high-frequency oscillatory ventilation; $pCO_2$, partial pressure of carbon dioxide; sNIPPV, synchronized nasal intermittent positive pressure ventilation.
Note: Data are presented as means ± standard deviations.
[a]Assuming no carryover effect exists.
[b]Assuming no sequence effect exists.

 

than those during nHFOV by 2 mm Hg, this difference was inconsistent and not clinically significant (►Fig. 2). Further research on nHFOV and sNIPPV is needed in larger samples. Finally, the results of this study should be interpreted with caution, as neonatal units have patients with different demographics, use different types of ventilators, and have different NIV management protocols. The generalizability of our results should be verified in multicenter studies.

In conclusion, the sNIPPV mode was associated with a lower $pCO_2$ level than the nHFOV mode. However, the $pCO_2$ level did not significantly differ in preterm and very preterm neonates. Further research on the $pCO_2$ level and reintubation resulting from nHFOV and sNIPPV with different respiratory settings is needed to develop standardized protocols for extubated neonates.

## Clinical Trial Registration

This trial has been registered in the ClinicalTrials.gov database (*https://clinicaltrials.gov/ct2/show/NCT04323397*). First posted registration: March 26, 2020.

## Note

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the institutional ethics committee. Written informed consent was obtained from all participants.

## Authors' Contributions

K.B., M.P., and A.T. designed the data collection instruments, collected data, performed the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. A.T., G.M., S.D., and W.J. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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## Conflict of Interest

None declared.

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