The Effect of Noninvasive High-Frequency Oscillatory Ventilation on Desaturations and Bradycardia in Very Preterm Infants: A Randomized Crossover Trial

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Noninvasive high-frequency oscillatory ventilation compared with nasal continuous positive airway pressure significantly reduced the number of desaturations and bradycardia in preterm infants. However, noninvasive high-frequency oscillatory ventilation was associated with increased oxygen requirements and higher heart rates. *(J Pediatr 2018;■■:■■-■■).*

Trial registration Australian and New Zealand Clinical Trial Registry: ACTRN12616001516471.

Intermittent episodes of desaturation and bradycardia are common in preterm infants and related to cardiorespiratory instability and immaturity of respiratory control.[1,2] Evidence suggests that frequent prolonged desaturation episodes are associated with adverse neurologic outcome.[3] Caffeine and nasal continuous positive airway pressure (nCPAP) are effective at decreasing the frequency and severity of these episodes.[4] However, some infants require escalation of respiratory support to mechanical ventilation via an endotracheal tube, which is associated with bronchopulmonary dysplasia, a strong predictor of neurologic impairment.[5,6]

Noninvasive high-frequency oscillatory ventilation (nHFOV) is a new method of augmenting nCPAP support in preterm infants, potentially combining the advantages of both invasive high-frequency oscillatory ventilation and nCPAP.[7,8] Even though nHFOV is increasingly used, data on clinical efficacy and safety are limited. In the current study, we tested the hypothesis that, in preterm infants born at <30 weeks of gestation, nHFOV compared with nCPAP would reduce the combined number of episodes of desaturation (peripheral oxygen saturation [SpO_2] of <80%) and bradycardia (heart rate of <80 bpm).

Methods

This prospective, randomized, crossover trial in the neonatal intensive care unit of The Royal Women's Hospital, Melbourne was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616001516471) and approved by the ethics committee. Prospective written informed parental consent was provided. Infants were eligible if they were born <30 weeks of gestation, extubated for >24 hours and receiving nCPAP support, >7 days of age, and between 26 and 34 completed weeks of gestation at the time of study.

Each intervention period was 120 minutes, which was preceded by a 30-minute washout period on the assigned therapy. Nasal HFOV was commenced at a mean airway pressure (MAP) equal to the nCPAP pressure in use before the study, at an inspiratory to expiratory ratio of 50%, and a frequency of 8 Hz. The latter was identified as the optimal rate for gas exchange in a test lung.[9] Adjustments to the MAP and frequency were not permitted. The oscillatory amplitude was set at 20 cm H_2O and adjusted (±2 cm H_2O every 2 minutes),[7] to maintain normocapnic transcutaneous carbon dioxide ($tcCO_2$) levels (40-60 mm Hg). Nasal HFOV failure was defined by the presence of at least one of the following criteria: $tcCO_2$ measurements of >75 or <30 mm Hg, increase in the fraction of inspired oxygen (FiO_2) by ≥0.25 from baseline, or >2 apneas requiring stimulation per hour. If nHFOV treatment failure occurred, infants were switched back to nCPAP at the settings used before study entry.

Nasal CPAP was kept at the same set pressure level in use before the start of the study. In both intervention periods, FiO_2 was adjusted to maintain SpO_2 levels in the recommended range (91%-95%). Infants were fed via an orogastric tube at the start of each intervention period and handling was minimized throughout the study.

FiO_2	Fraction of inspired oxygen
MAP	Mean airway pressure
nCPAP	Nasal continuous positive airway pressure
nHFOV	Noninvasive high-frequency oscillatory ventilation
SpO_2	Peripheral oxygen saturation
$tcCO_2$	Transcutaneous carbon dioxide

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The primary outcome was the paired difference in the combined number of episodes of desaturation and bradycardia during the 120-minute recording periods for each intervention. A desaturation was defined as a decrease in SpO_2 of <80% for >2 seconds. Desaturation episodes separated by ≤2 seconds were counted as a single episode. A bradycardic episode was defined similarly using a cutoff of 80 bpm. Episodes of simultaneous desaturation and bradycardia were counted as a single episode.

Secondary outcomes included the paired differences of the following measures: FiO_2, SpO_2, heart rate, respiratory rate, absolute time, and proportion of time with an SpO_2 of <80%, number of desaturations with an SpO_2 of <80% and <60%, number of desaturations to <80% for >10 seconds, and number of bradycardic episodes with a heart rate of <100 bpm and <60 bpm. Safety-related events (nasal trauma, gaseous distention of the abdomen, and feed intolerance defined as gastric residuals or vomiting) and signs of discomfort (tachycardia >190 bpm that cannot be explained by concomitant changes in hemodynamics or oxygen transport) were evaluated during both interventions. We assessed the following additional outcomes during the nHFOV period; $tcCO_2$ measurements, $tcCO_2$ readings of <30 mm Hg (hypocapnia) or >60 mm Hg (hypercapnia), and the number of changes in oscillation amplitude.

A Babylog VN500 ventilator (Dräger Medical System, Lübeck, Germany) and short binasal prongs (Hudson Respiratory Care, Temecula, California) were used for both intervention periods. SpO_2 levels and heart rate were measured using a pulse oximeter (Radical7 V5; Masimo, Irvine, California) with a 2-second averaging time. The FiO_2 was measured using an oxygen analyzer (AX300, Teledyne Analytical Instruments, City of Industry, California) inserted into the inspiratory limb of the ventilator. All signals were continuously recorded at 200 Hz using the NewLifeBox Neo-RSD physiological monitor (Advanced Life Diagnostics UG, Weener, Germany). Immediately before commencement of nHFOV, a $tcCO_2$ transducer (Philips M1018A module, Philips Electronics, Andover, Massachusetts) was placed on the infant's skin. When $tcCO_2$ readings stabilized, a capillary blood gas sample was taken. Transcutaneous CO_2 values were recorded manually every minute for the first 10 minutes and every 5 minutes thereafter. After 90 minutes of recording time, the $tcCO_2$ transducer was removed to protect the infant's skin from prolonged application of heat.

We calculated the required sample size (45 patients) based on effect size, assuming that nHFOV was 0.6 SD better than nCPAP. In a planned interim analysis after enrollment of the first 20 patients, the mean number of episodes in the nCPAP group was 17 and the SD of the paired difference was 10. A recalculation of the sample size revealed that 40 infants were required to detect a decrease from 17.0 to 13.5 episodes when infants were changed from nCPAP to nHFOV with 80% power and an α-error of 0.05.[10]

A computer-generated randomization sequence with variable block sizes and sequentially numbered, sealed, opaque envelopes containing the sequence allocation were used. Blinding of caregivers to the intervention was not possible. For each outcome variable, the paired difference between the 2 interventions (nHFOV minus nCPAP) was calculated. If the paired differences were normally distributed, data were presented as means (SD) and compared using a 2-tailed paired *t*-test. If the distributions were skewed, medians (IQR) and a Wilcoxon matched pairs test were presented. One-way repeated measures ANOVA was used for $tcCO_2$ differences over time. $P < .05$ was considered significant. All analyses were performed using Stata/IC software, version 15.1 (SataCorp, College Station, Texas).

Results

Of the 42 infants recruited between November 17, 2016, and November 16, 2017, data from 40 infants were analyzed (**Figure 1**; available at www.jpeds.com). Demographic and clinical characteristics are given in **Table I**.

The median (IQR) number of episodes of desaturation and bradycardia was 5.5 (0.5-13.5) during nHFOV and 8.5 (1.0-25.0) during nCPAP (paired difference, −1.0; IQR, −8.5 to 0.0; $P = .001$). During nHFOV, episodes decreased in 25 infants (63%), increased in 7 infants (17%), and remained unchanged in 8 infants (20%). Five infants (13%) did not have any episodes during either intervention period (**Figure 2**; available at www.jpeds.com). No infants met the criteria for nHFOV failure.

There were no differences in the mean SpO_2 or respiratory rate. During nHFOV, infants had higher FiO_2 and higher heart rates (**Table II**). Nasal HFOV did not result in substantial changes in the mean $tcCO_2$ ($P = .36$). The mean (SD) $tcCO_2$ was 52.1 (7.9) mm Hg immediately before the start of nHFOV when the infants were still on nCPAP support and 49.1 (9.5) mm Hg after 90 minutes of nHFOV. Hypercapnia was present in 10 infants (25%; maximum $tcCO_2$, 73 mm Hg), 6 (60%) of whom were hypercapnic when nHFOV started. The oscillation amplitude was increased on 66 occasions (maximum amplitude,

Table I. Baseline demographic and clinical characteristics

Characteristics	All infants (n = 40)
Perinatal	
Antenatal glucocorticoids, n (%)	36 (90)
Gestational age at birth, wk	26.5 ± 1.5
Birthweight, g	881 ± 181
Male, n (%)	22 (55)
Median Apgar score at 5 min (IQR)*	8 (6-8)
Exogenous surfactant, n (%)	37 (93)
Before randomization	
Postnatal glucocorticoids, n (%)	14 (35)
Median duration of endotracheal ventilation (IQR), d	10 (2-32)
Median duration of noninvasive ventilation (IQR), days	11 (9-19)
At randomization	
Median postnatal age (IQR), d	33 (16-45)
Corrected age, wk	31.0 ± 1.5
Weight, g	1329 ± 318
Underwater "bubble" CPAP system, n (%)	38 (95)
Nasal CPAP pressure, cm H_2O	7.1 ± 1.2
FiO_2	0.30 ± .07
Median caffeine dose (IQR), mg/kg/d	8 (8-10)

Plus–minus values are means ± SD.
*The Apgar score was not known in 2 infants.

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Table II. Primary and secondary outcomes

	nHFOV		nCPAP		Paired difference	
	Total*	Median (IQR)	Total*	Median (IQR)	Median (IQR)	*P*
Primary outcomes						
Number of episodes†	538	5.5 (0.5 to 13.5)	658	8.5 (1.0 to 25.0)	−1.0 (−8.5 to 0.0)	.001
Desaturation <80% (n)	536	5.0 (0.5 to 13.5)	652	8.5 (1.0 to 25.0)	−1.0 (−8.5 to 0.0)	.002
Bradycardia <80 bpm (n)	5	0.0 (0.0 to 0.0)	19	0.0 (0.0 to 1.0)	0.0 (−1.0 to 0.0)	.004
Secondary outcomes						
Desaturation <80%, >10 s (n)	99	0.5 (0.0 to 2.0)	130	1.0 (0.0 to 4.0)	0.0 (−2.5 to 0.0)	.03
Desaturation <60% (n)	28	0.0 (0.0 to 0.0)	49	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	.47
Hypoxemia <80% (minutes)	75	0.63 (0.06 to 1.59)	99	0.99 (0.10 to 3.23)	−0.04 (−1.14 to 0.08)	.05
Hypoxemia <80% (%)	N/A	0.52 (0.05 to 1.32)	N/A	0.82 (0.08 to 2.70)	0.00 (−0.95 to 0.07)	.05
Bradycardia <60 bpm (n)	2	0.0 (0.0 to 0.0)	3	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	.32
Bradycardia <100 bpm (n)	15	0.0 (0.0 to 1.0)	51	0.0 (0.0 to 2.0)	0.0 (−1.5 to 0.0)	.01
Vital signs	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**	***P***
Respiratory rate (min^{-1})‡	67 ± 19		65 ± 16		2 ± 16	.41
Heart rate (bpm)	170 ± 8		166 ± 8		4 ± 8	.01
Oxygen saturation (%)	93.1 ± 2.1		93.4 ± 2.3		−0.3 ± 1.5	.25
FiO_2	0.31 ± 0.09		0.28 ± 0.08		0.03 ± 0.03	<.001

*Across all 40 infants.
†The total number of desaturations and bradycardias do not add up to the total number of episodes because episodes of simultaneous desaturation and bradycardia were counted as single episodes.
‡Respiratory rate available for 32 infants.

40 cm H_2O). On 52 occasions (79%) this change did not result in a reduced carbon dioxide level over the following 10 minutes. None of the infants were hypocapnic. In 6 infants (15%) and on 7 occasions the amplitude was decreased owing to tachycardia with heart rates of >190 bpm. The tachycardia resolved in all infants when the amplitude was decreased. During nHFOV, no infants developed nasal trauma, gaseous distention of the abdomen, or feed intolerance.

Discussion

In this randomized crossover trial, nHFOV compared with nCPAP resulted in a significant decrease in the number of episodes of desaturation and bradycardia. Although no change in oxygen saturation levels between the interventions was noted, infants had higher oxygen requirements and higher heart rates during nHFOV. Using the same airway pressure with a fixed frequency, nHFOV did not improve carbon dioxide clearance in this stable patient population. Noninvasive HFOV was generally well-tolerated; however, the oscillation amplitude had to be decreased in some infants owing to changes that were deemed to be consistent with discomfort.

Various effects of the oscillating pressure may explain the decrease in the number of desaturations and bradycardia. Pressure oscillations may improve surfactant function, stabilize peripheral airways, and, in contrast with noninvasive pressure support ventilation, maintain inspiratory glottic dilator activity.[11-13] Transmission of pressure oscillations to the oropharynx may increase the drive to the upper airway muscles and maintain patency of the upper airway, which is believed to be the primary site of airway obstruction leading to desaturations in the neonate.[14] Interestingly, a suppression of central respiratory drive in lambs was observed when nHFOV was applied at a very low frequency of 4 Hz.[13] Our findings in preterm infants are reassuring; we applied nHFOV with a frequency of 8 Hz and did not observe an inhibition of spontaneous breathing.

The use of nHFOV has been evaluated in bench and animal models[9,15-17] and in 3 randomized clinical studies in preterm infants,[18-20] but none were designed to look at differences in rates of desaturation and bradycardia. Our results contrast with those reported in a recent study in which the number of apneas and bradycardia was a secondary outcome and not different between interventions ($P = .10$ for apnea and $P = .14$ for bradycardia).[18] Our findings, however, are in line with those obtained in a retrospective case series which reported significant reductions in the mean (SD) number of episodes from 3.2 (0.4) to 1.2 (0.3) per hour with nHFOV ($P < .001$).[21]

Carbon dioxide clearance was reported in 2 of the 3 randomized studies.[18,19] Nasal HFOV was compared with nCPAP or biphasic nCPAP with the same MAP set for both intervention periods. Their finding of no increased carbon dioxide clearance with nHFOV was similar to our results. This finding is in contrast to observational studies in infants with evolving bronchopulmonary dysplasia that suggested superior carbon dioxide elimination using nHFOV compared with nCPAP.[21-24] In 3 of those studies, however, MAPs were higher during nHFOV than during nCPAP. Thus, the higher airway pressure, rather than the pressure waveform, may have resulted in the observed benefit. This finding is consistent with our observation, namely, that increasing the oscillation amplitude did not increase CO_2 clearance despite this being suggested by benchtop models of nHFOV.[25] However, we adjusted the oscillation amplitude to optimize chest vibration, which may not be appropriate for infants without severe lung disease. Moreover, we did not attempt to avoid oral gas leak in our study, because a moderate leak has been shown to improve rather than impair gas exchange during nHFOV.[26] A large leak may have been present in some infants and may have impaired pressure

amplitude transmission. Finally, short binasal prongs were used in our study and it is likely that different nasal interfaces may also impact gas exchange during nHFOV.

For most infants, changes in the primary outcome were of small to moderate size. Where a clinically important difference occurred, this more often favored nHFOV. There was 1 outlier in terms of both direction and magnitude of the change (**Figure 2**). This infant was born at 26 weeks of gestation, was postnatal day 33, had never been intubated, and was receiving 10 cm H_2O nCPAP with an FiO_2 of 0.35 for evolving bronchopulmonary dysplasia. He was randomized to receive nCPAP first. His total number of episodes of desaturation (without bradycardia) was 29 during nCPAP and 117 during nHFOV (paired difference, 88). Most of his episodes were caused by undulating oxygen saturation levels with brief drops to <80%. Inclusion of this infant's data resulted in a skewed distribution of the paired difference. If this infant was excluded, the mean (SD) number of episodes would have been 10.8 (17.1) during nHFOV and 16.1 (19.5) during nCPAP (paired difference, −5.3 [9.2]; $P = .001$). It is possible that this infant did respond poorly to nHFOV. Alternatively, he may have had a period of instability unrelated to the method of respiratory support, for example, feed intolerance or airway obstruction.

Noninvasive HFOV seems to be promising and raises the question of how clinicians can select infants who may benefit most from this mode of support. Infants with a low number of episodes are not likely to gain any advantage from nHFOV, whereas infants with a high rate of episodes are more likely to benefit. However, in our study, the 2 infants with the highest event rates deteriorated during nHFOV and we remain uncertain as to whether the addition of oscillations to unstable infants is beneficial or harmful. With the current level of evidence available, we would argue for the cautious use of nHFOV in this group of preterm infants. It may be justified on a case-by-case basis when intubation for desaturations and bradycardia is imminent.

Our study has some limitations. The included infants were mostly stable on noninvasive respiratory support. This might not reflect current clinical practice, where nCPAP failure was the most common indication for nHFOV.[21,27] Randomizing preterm infants being extubated from mechanical ventilation, or when failing nCPAP, to either noninvasive intermittent positive pressure ventilation or nHFOV may have drawn a more relevant picture of the potential clinical usefulness of nHFOV. The use of nHFOV was restricted to 120 minutes and, thus, only short-term outcomes are reported. The long-term safety of nHFOV remains unknown. Short time frames for the definition of our primary outcome were used; the clinical relevance of such brief drops in SpO_2 and heart rate is unclear. Our study does not adequately address the capability of nHFOV to wash out carbon dioxide owing to the chosen population and study protocol. Greater effects may have been observed in sicker infants with chronic lung disease. Although patient comfort has been addressed in our trial, the use of a pain scoring system is lacking. Validated measures of discomfort should be implemented in any future nHFOV trial. Last, outcome assessors were not blinded to the intervention.

In conclusion, nHFOV in very preterm infants is feasible and in the majority of cases is associated with a significant decrease in the number of desaturations and bradycardia. However, in view of changes in heart rate and oxygen requirement during the 120 minutes of nHFOV, adequately powered randomized, controlled trials are warranted to evaluate appropriate clinical indications, optimal settings and safety in the neonatal population. ■

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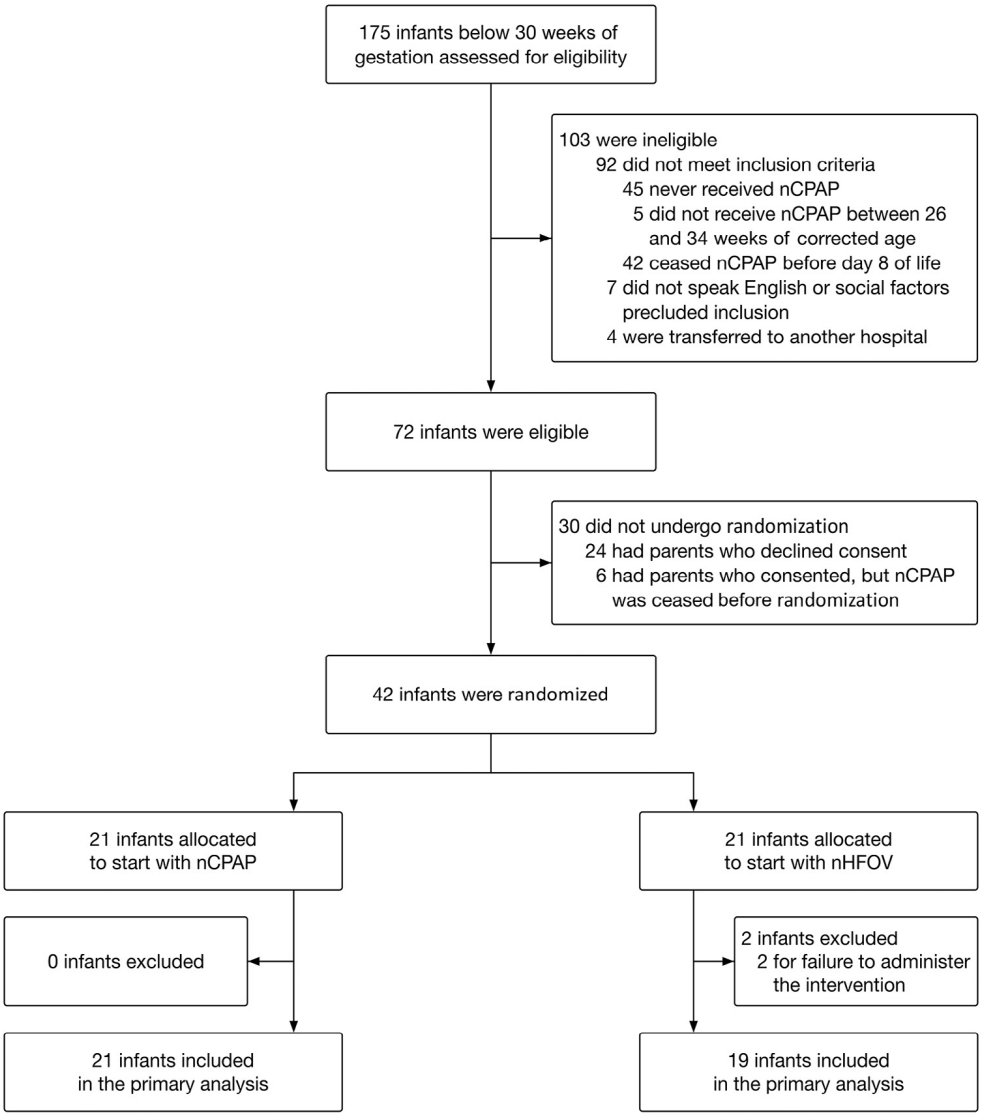

Figure 1. Flowchart (CONSORT diagram) showing the numbers of infants who were screened, assigned to an interventional sequence, and included in the primary analysis.

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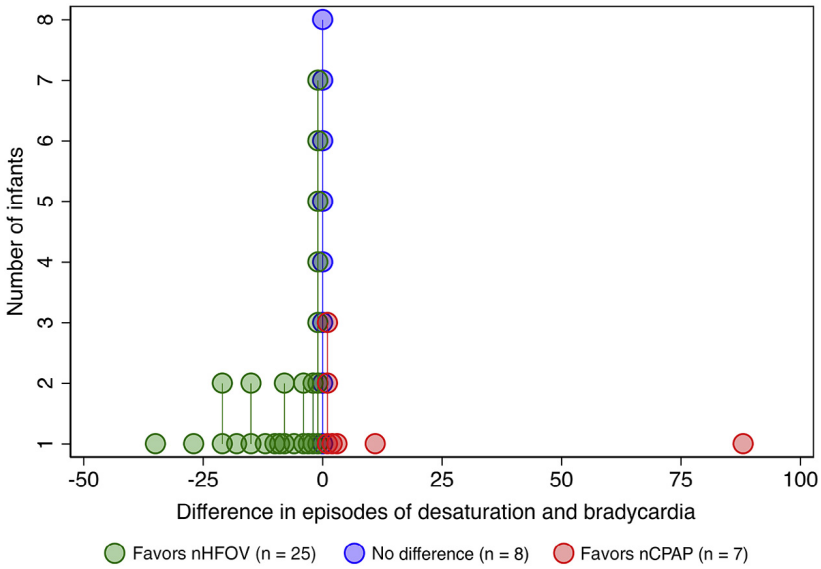

Figure 2. Difference in the number of episodes of desaturation and bradycardia between nHFOV and nCPAP. Each dot represents a single infant.

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