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;■■:■■-■■).*

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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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