CHEST

# Nasal High-Frequency Oscillatory Ventilation in Preterm Infants With Respiratory Distress Syndrome and ARDS After Extubation

## A Randomized Controlled Trial

*Long Chen, PhD, MD; Li Wang, PhD, MD; Juan Ma, MD; Zhichun Feng, PhD, MD; Jie Li, MD; and Yuan Shi, PhD, MD*

**BACKGROUND:** Nasal high-frequency oscillatory ventilation (NHFOV) has been described as supplying the combined advantages of nasal CPAP (NCPAP) and HFOV. However, its effect on preterm infants needs to be further elucidated. Our objective was to assess whether NHFOV could reduce intubation and $P_{CO_2}$ levels as compared with NCPAP during the postextubation phase in preterm infants.

**METHODS:** This was a single-center, randomized, controlled trial, and it was registered at clinicaltrials.gov (NCT03140891) and conducted between May 2017 and May 2018. Ventilated infants born at less than 37 weeks' gestational age and ready to be extubated were included and randomized to either the NHFOV or NCPAP group. Primary outcomes were the incidence of reintubation within 1 week and the $P_{CO_2}$ level within 6 h.

**RESULTS:** A total of 206 preterm infants were included. Of them, 127 (61.7%) were diagnosed with respiratory distress syndrome, 53 (25.7%) with ARDS, and 26 (12.6%) with both respiratory distress syndrome and ARDS. Comparing with NCPAP, NHFOV significantly reduced the reintubation rate (16:87 vs 35:68; 95% CI, 0.18-0.70; $P = .002$), especially in the subgroup with a gestational age of ≤ 32 weeks (12:34 vs 25:20; 95% CI, 0.12-0.68; $P = .004$). The $P_{CO_2}$ level was also significant lower in the NHFOV group (49.6 ± 8.7 vs 56.9 ± 9.9; 95% CI, –9.95 to –4.80; $P = < .001$). Moreover, NHFOV significantly reduced the reintubation rate in preterm infants with ARDS (10:33 vs 21:15; 95% CI, 0.08-0.57; $P = .002$).

**CONCLUSIONS:** NHFOV was shown to be superior to NCPAP in avoiding reintubation, especially in very preterm infants and those infants diagnosed with ARDS.

**TRIAL REGISTRY:** ClinicalTrials.gov; No.: NCT03140891; URL: www.clinicaltrials.gov

CHEST 2019; 155(4):740-748

**KEY WORDS:** ARDS; nasal CPAP; nasal high-frequency oscillatory ventilation; preterm infant; respiratory distress syndrome

**ABBREVIATIONS:** BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; MAP = mean airway pressure; NCPAP = nasal CPAP; NHFOV = nasal high-frequency oscillatory ventilation; NICU = neonatal ICU; NIPPV = nasal intermittent positive-pressure ventilation; RDS = respiratory distress syndrome

**AFFILIATIONS:** From Department of Neonatology (Drs Chen and Shi), Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China; China International Science and Technology Cooperation Base of Child Development and Critical Disorders (Drs Chen and Shi), Chongqing, China; Chongqing Key Laboratory of Pediatrics (Drs Chen and Shi), Chongqing, China; Department of Pediatrics (Drs Wang, Ma, and Shi), Daping Hospital of the Army Medical University, Chongqing, China; the Affiliated BaYi Children's Hospital (Dr Feng), PLA Army General Hospital, Beijing, China; and Department of Obstetrics and Gynecology (Dr Li), The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

J. L. and Y. S. made equal contributions to the present study.

Invasive ventilation remains one key cornerstone to reduce neonatal mortality in preterm infants with respiratory distres syndrome (RDS) and/or ARDS. However, it is also related to increased risks of ventilator-associated lung injury and escalation of pulmonary inflammation, which finally result in bronchopulmonary dysplasia (BPD),[1] and later in neurologic impairment among the survivors,[2-4] especially in those infants with repeated intubation and/or prolonged duration of invasive ventilation. Early weaning from invasive ventilation is therefore a key procedure to reduce these risks.

Besides caffeine,[5] early noninvasive respiratory support strategies have been suggested to be the most effective pathways to reduce short- and long-term mortality and morbidity. Nasal CPAP (NCPAP) was one widely used noninvasive ventilation strategy in preterm infants. However, there was only a 60% success rate in avoiding intubation.[6] One of the important causes was the increased $P_{CO_2}$.[7] By combining the advantages of NCPAP and high-frequency oscillatory ventilation (HFOV) with high $CO_2$ removal, there was no need for synchronization; it was noninvasive; the lower volume required resulted in fewer barotraumas; and functional residual capacity was increased.[8] Nasal HFOV (NHFOV) was considered a strengthened version of NCPAP. Furthermore, the superimposed oscillations of NHFOV avoided gas trapping and clearly allowed the upregulation of mean airway pressure (MAP) compared with NCPAP. Thus, NHFOV might be more beneficial as a postextubation respiratory support strategy to avoid reintubation and subsequent complications and/or sequelae as compared with NCPAP in preterm infants.[9] Nowadays, NHFOV is increasingly used in neonatal ICUs (NICUs) around the world because of its convenient operation. A retrospective review has reported some beneficial effects of NHFOV in preterm infants as a remedial measure after other noninvasive modes have failed, including reducing the number of apneas, bradycardias, and oxygen desaturations.[10] New diagnostic criteria for pediatric and neonatal ARDS were proposed in 2015[11] and 2017.[12] However, there were rare randomized controlled studies comparing NHFOV with NCPAP in preterm infants with RDS and/or ARDS.[13-16]

We have found that NHFOV as the primary respiratory support strategy was associated with a decreased rate of intubation as compared with NCPAP in a Chinese single-center, randomized controlled trial.[17] The purpose of the present study was to compare NHFOV with NCPAP as postextubation respiratory support strategies for endotracheal ventilation, as well as the $P_{CO_2}$ level, in preterm infants.

## Patients and Methods

### Standard Protocol Approval, Registration, and Patient Consent

This study was approved by the Ethics Committee of Daping Hospital of the Army Medical University (project approval No. 201716) and registered at https://www.clinicaltrials.gov (clinicaltrials.gov; Identifier: NCT03140891) (registration date, May 3, 2017). The study was designed to be a prospective protocol, and informed parental written consent was obtained prior to the start of the study. The trial was performed in accordance with the approved guidelines and regulations of the participating institutions. Additional details can be found in e-Appendix 1.

### Study Design and Participants

This was a single-center, randomized controlled trial conducted in a tertiary NICU from May 2017 to May 2018, at Daping Hospital of the Army Medical University at Chongqing, China.

Eligibility requirements for neonates were as follows: (1) The gestational age was less than 37 weeks; (2) the preterm neonates were diagnosed with RDS- and/or ARDS-associated respiratory failure, and supported by invasive ventilation with synchronized intermittent mandatory ventilation or HFOV; (3) there were no intraventricular hemorrhage (IVH) grade 3 or 4; and (4) the first extubation and subsequent noninvasive ventilation were ready to be carried out.

Exclusion criteria were as follows: (1) parents' decision not to participate; and (2) major congenital anomalies.

### Definition of the Important Diagnoses and Concepts

**Diagnosis of RDS:** The clinical signs and symptoms, including respiratory distress, tachypnea, nasal flaring, groan, and cyanosis, appeared within 24 h of birth, as well as an effective response to pulmonary surfactant and/or lung recruitment strategies. Other criteria included typical radiographic features such as a grainy shadow, air bronchogram, or white lungs.

**Diagnosis of ARDS:** The diagnosis of ARDS was made according to the criteria established by the Pediatric Acute Lung Injury Consensus Conference Group in 2015[11] and a Montreux conference in 2017.[12]

**FUNDING/SUPPORT:** This study was supported by Social Livelihood Program of the Chongqing Science and Technology Commission, China (No. cstc2018jscx-msybX0040).

**CORRESPONDENCE TO:** Yuan Shi, PhD, MD, Department of Neonatology, Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, No. 136, Zhongshanger Rd, Yuzhong District, Chongqing, 400014, China; e-mail: shiyuan@hospital.cqmu.edu.cn



**DOI:** https://doi.org/10.1016/j.chest.2019.01.014

In addition, the causes of ARDS included mainly sepsis, meconium aspiration syndrome, pneumonia, bile pneumonia, and milk aspiration.

### Eligibility Criteria for Extubation

The respiratory support mode before extubation was synchronized intermittent mandatory ventilation. Besides the improved symptoms, radiographs, and sufficient spontaneous breathing efforts, the eligibility criteria for extubation included a peak inspiratory pressure of 15 to 25 cm $H_2O$, a positive end-expiratory pressure of 4 to 6 cm $H_2O$, a respiratory rate of 10 to 30, an $FIO_2$ from 0.21 to 0.30, and a hematocrit exceeding 35%.[18] Arterial blood gas analysis was needed to meet the following criteria: pH $> 7.20$, $PaCO_2 \leq 55$ mm Hg.

### Allocation and Blinding

Allocation was carried out according to a similar methodology used in another study.[17] After documenting parental consent, the infants with invasive ventilation were randomly assigned to either NHFOV or NCPAP, using a table of random numbers and sealed opaque envelopes when they were eligible for extubation. Blinding to doctor was not possible, due to the nature of the intervention.

### Administration of Caffeine Citrate and Pulmonary Surfactant Replacement

These preterm infants received caffeine citrate at a loading dose of 20 mg/kg and a maintenance dose of 10 mg/kg/d until 34 weeks of gestational age.

Pulmonary surfactant (poractant alfa [Curosurf]; Chiesi Pharmaceuticals) was administered at a dose of 100 mg/kg as a rescue treatment if an infant needed $FIO_2 > 0.40$ to maintain the targeted oxygen saturation ($SpO_2$). The intervals of surfactant administration were 6 to 12 h; no more than four doses were allowed.

### Study Intervention

When the neonate had fulfilled the extubation criteria, NHFOV or NCPAP was immediately started on the basis of the group assignment. Other care was at the discretion of the attending neonatologist.

A time-cycled, pressure-limited, and continuous-flow neonatal ventilator (SLE5000; SLE) was used for neonates assigned to the NHFOV group. The initial settings were as follows: (1) a frequency of 10 Hz (subsequent regulation range, 8-12, in steps of 1 Hz); (2) an inspiratory time of 50% (1:1)[19]; (3) an oscillation amplitude of 35 cm $H_2O$ (subsequent regulation range, 25-50, in steps of 5 cm $H_2O$).[14,19] Oscillation amplitude would be regulated according to the level of $PCO_2$. Visible chest oscillation was not necessary because elimination of $CO_2$ during NHFOV could also occur in the upper respiratory airway deadspace.[20] Hypercarbia was one of the most important causes of reintubation, and therefore amplitude would first be upregulated, and then frequency would be lowered within the above-restricted ranges to avoid hypercarbia[21]; (4) an MAP of 10 cm $H_2O$ (subsequent regulation range, 5-16, in steps of 1 cm $H_2O$).[8] MAP was regulated according to an open lung recruitment strategy[22]; and (5) $FIO_2$ regulated from 0.21 to 0.40 (target value, $\leq$ 30%) in order to maintain $SpO_2$ from 90% to 95% as determined with a pulse oximeter.

Neonates assigned to NCPAP were initiated at a pressure of 6 cm $H_2O$ (subsequent regulation range, 4-8, in steps of 1 cm $H_2O$) with a bubble CPAP system (Fritz Stephan GmbH), with $FIO_2$ from 0.21 to 0.40 (target value, $\leq$ 30%) to maintain $SpO_2$ from 90% to 95%.

NHFOV and CPAP would be connected to preterm infants through short binasal prongs (short tubes that fit in both nostrils).[23] The size of the nasal prongs would be selected according to the nares' diameter and manufacturer's instructions.

To avoid stomach/intestine dilation, a tube was used from mouth to stomach and gas was periodically aspirated in both groups when the interventions were conducted.

To reduce neonates' discomfort and gas leak, nursing, pacifiers, and positioning should be used. Otherwise, no oral or injected sedation was applied.

### Eligibility Criteria for Reintubation

The subjects would be reintubated if they did not improve and needed invasive ventilation, the determination of which was based on the standard indications used in another study.[24] The criteria for reintubation and mechanical ventilation were met with the occurrence of any one of the following conditions: (1) cardiorespiratory arrest or any type of pulmonary hemorrhage; (2) 2 h of respiratory acidosis with $PaCO_2 > 70$ mm Hg and pH $< 7.2$; (3) 2 h of hypoxia with $PO_2 <$ 50 mm Hg, $FIO_2$ less than 0.6, and maximal pressures given (8 and 16 cm $H_2O$ in the NCPAP group and NHFOV group, respectively); (4) apnea occurring three or more times per hour and a heart rate less than 100/min; (5) requirement for mask ventilation in any case; and (6) persistent low blood pressure without response to liquid resuscitation and vasoactive agents.

If a preterm infant failed the first extubation, the noninvasive supporting mode of the second extubation was at the discretion of the attending neonatologist.

### Weaning From NHFOV and NCPAP Interventions

The study intervention would be stopped according to clinical conditions and the following criteria for 24 to 48 h: (1) weaning from NCPAP: pressure would be reduced by 1-cm $H_2O$ steps down to a minimum of 4 cm $H_2O$, with $FIO_2$ at less than 25%; (2) weaning from NHFOV: amplitude would be reduced to the minimum initial level of 25 cm $H_2O$ and MAP would be reduced by 1 cm $H_2O$ down to a minimum of 5 cm $H_2O$, with $FIO_2$ at less than 25%.

### Termination of the Study

The study would end if one of the following conditions was reached: (1) death; (2) parents' decision not to continue participating; or (3) discharge according to doctors' suggestions.

### Primary and Secondary Outcomes

The primary outcomes of this study were to determine the need for endotracheal ventilation within 1 week and the level of $PCO_2$ within 6 h in preterm infants randomized to NCPAP or NHFOV. $PCO_2$ levels were determined by arterial or arterialized blood gas analysis.

The secondary outcomes included the incidences of BPD, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, and IVH, as well as hospital stay, abdominal distention, and nasal trauma.

Ultrasound was used to assess cardiac morphology, pulmonary pressures, and patent ductus arteriosus within the first 24 h of life, and was subsequently repeated every week until recovery/leaving hospital. Cerebral ultrasound was performed within 72 h of life and subsequently repeated every week until recovery or discharge. Other routine therapies, including preventing BPD, routine fluid administration, and nutritional supplementation, were done according to Chinese guidelines. The diagnosis of BPD was consistent with the National Institute of Child Health and Human Development definition.

### Sample Size Estimation

Sample size estimation was calculated with PASS software (2008, version 8.0.3; NCSS). According to previous studies,[6] an average of 40% of preterm neonates administered NCPAP after extubation needed endotracheal ventilation. A systematic review has shown that nasal intermittent positive-pressure ventilation (NIPPV) reduced the incidence of extubation failure and the need for reintubation within 48 h to 1 week more effectively than NCPAP.[25] Although no study compared NHFOV with NIPPV, NHFOV was quite widely used in some European countries[26] and could be beneficial as a rescue strategy after another noninvasive mode, including NIPPV.[10,20] A reasonable hypothesis was that NHFOV could be noninferior to NIPPV in avoiding reintubation. Our previous study has indicated that the success rate of NIPPV was about 85%[27]; NHFOV was therefore thought to provide no less than an 85% success rate. A plausible estimate of the coincidence rate of both NHFOV and NCPAP success was 70%, and with 80% power and a two-sided significance level of .05, 71 neonates at least would be needed in each group.

In actuality, our study also showed that the success rate of NCPAP was about 76%.[27] We calculated the sample size, expecting a 15% increase in NHFOV. With 80% power and a two-sided significance level of .05, 101 infants would be needed in each group. Considering the gestational age differences of the two studies (26 vs < 37 weeks),[6,27] a minimum sample size of 101 was needed in each group.

### Statistical Analysis

Independent continuous variables, expressed as mean ± SD, were analyzed by *t* test. Categorical variables were analyzed by $\chi^2$ test or Fisher test. The two subgroups were predefined as ≤ 32 weeks and 32 to $36^{+6}$ weeks, and subgroup analyses were conducted for the primary outcomes. Moreover, to further justify the effect of RDS and/or ARDS on reintubation within subgroups, a test of diagnosis-by-gestational age subgroup interaction was conducted using binary logistic regression. All analyses were carried out with computer software (SPSS 16.0 for Windows; IBM). A *P* value less than .05 was regarded as statistically significant.

## Results

### Study Neonates

A total of 262 preterm infants were screened between May 4, 2017 and May 30, 2018, of which 35 did not meet inclusion criteria, 10 parents of preterm infants declined to participate, and 11 were excluded because of no availability of study device. Finally, 206 preterm infants underwent randomization and finished the trials (103 in the NHFOV group and 103 in the NCPAP group) and were included in the final analysis (Fig 1). The number of involved preterm infants reached the calculated sample size. Analysis according to the intention-to-treat principle was considered to be the most proper way of analyzing randomized controlled trial results. Data analyses followed the intention-to-treat principle. Intention-to-treat principle analysis required that all randomized participants be included and analyzed according to the treatment group to which they were originally assigned.

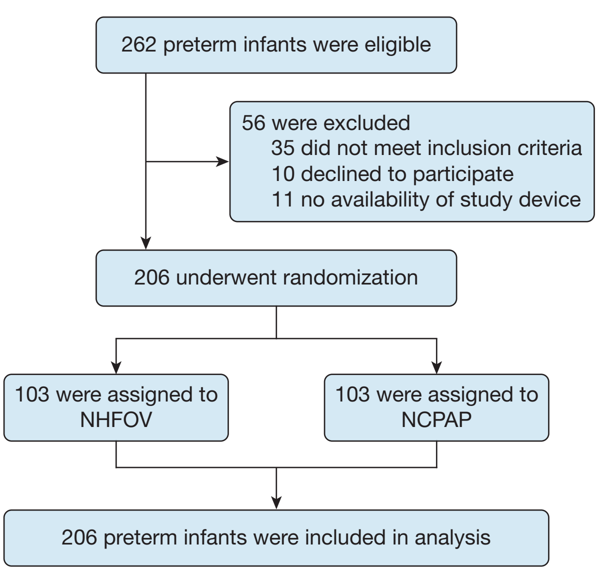


Figure 1 – *Flow diagram of participants through each stage.*

All neonates arrived at the NICU within 6 h. There were no significant differences in main clinical characteristics including birth weight, Apgar score, and sex between the two groups (Table 1). Seventy-five women (36.4%) received urgent cesarean delivery (41 in the NHFOV group and 34 in the NCPAP group), 77 (37.4%) underwent vaginal delivery (38 in the NHFOV group and 39 in the NCPAP group), and 54 (26.2%) received selective cesarean delivery (24 in the NHFOV group and 30 in the NCPAP group).

The main respiratory disorders were RDS and ARDS. Of the disorders, 127 (61.7%) were RDS (60 in the NHFOV group and 67 in the NCPAP group); 53 (25.7%) were ARDS, including 18 with sepsis (8.7%), 15 with meconium aspiration syndrome (MAS) (7.3%), 11 with pneumonia (5.3%), 8 with bile pneumonia (3.9%), and 1 with milk aspiration (0.5%). The other 26 (12.6%) were both RDS and ARDS (9 in the NHFOV group and 17 in the NCPAP group), in which ARDS due to sepsis was diagnosed.

### Primary and Secondary Outcomes

In the primary outcomes analysis (Table 2), both the rate of reintubation and $P_{CO_2}$ levels within 6 h were significantly lower in the NHFOV group than in the NCPAP group (reintubation: 16:87 vs 35:68, respectively; 95% CI, 0.18-0.70; $P = .002$) ($P_{CO_2}$ level: 49.6 ± 8.7 vs 56.9 ± 9.9, respectively; 95% CI, –9.95 to –4.80; $P = < .001$).

In the secondary outcomes analysis (Table 3), the hospital length of stay were found to be significantly shorter in the NHFOV group than in the NCPAP group (22.0 ± 14.3 vs 27.6 ± 17.1, respectively; 95% CI, –9.92

**TABLE 1 ]** Baseline Characteristics of Neonates in NHFOV and NCPAP Groups

| Characteristic | NHFOV (n = 103) | NCPAP (n = 103) | 95% CI | *P* Value |
|---|---|---|---|---|
| Gestational age, d | 226.8 ± 16.9 | 229.5 ± 16.8 | −7.27 to 2.01 | .265 |
| Sex (male), No. (%) | 59 (57.3) | 64 (62.1) | 0.46 to 1.43 | .478 |
| Birth weight, g | 1,859.1 ± 569.1 | 1,917.1 ± 477.9 | −202.35 to 86.43 | .430 |
| Apgar, 1 min | 8.2 ± 2.0 | 8.4 ± 1.9 | −0.83 to 0.24 | .315 |
| Apgar, 5 min | 8.9 ± 1.2 | 9.0 ± 1.1 | −0.42 to 0.22 | .548 |
| Apgar, 10 min | 9.2 ± 1.0 | 9.3 ± 1.0 | −0.41 to 0.14 | .326 |
| Antenatal corticoids (yes), No. (%) | 93 (90.3) | 92 (89.3) | 0.45 to 2.75 | .818 |
| Cesarean (yes), No. (%) | 65 (63.1) | 64 (62.1) | 0.59 to 1.83 | .885 |
| GDM (yes), No. (%) | 17 (16.5) | 24 (23.3) | 0.33 to 1.30 | .222 |
| Duration of invasive ventilation, d | 7.2 ± 3.4 | 7.8 ± 2.8 | −1.46 to 0.24 | .157 |
| Surfactant use (yes), No. (%) | 95 (92.2) | 88 (85.4) | 0.91 to 6.03 | .071 |
| PROM (yes), No. (%) | 43 (41.7) | 33 (32.0) | 0.86 to 2.69 | .149 |
| ICP (yes), No. (%) | 5 (4.9) | 7 (6.8) | 0.22 to 2.28 | .552 |
| $P_{CO_2}$ levels (before extubation), cm $H_2O$ | 44.1 ± 4.2 | 43.9 ± 4.5 | −1.01 to 1.39 | .750 |

GDM = gestational diabetes mellitus; ICP = intrahepatic cholestasis of pregnancy; NCPAP = nasal CPAP; NHFOV = nasal high-frequency oscillatory ventilation; PROM = premature rupture of the membrane.

to −1.27; *P* = .011). No other secondary outcomes significantly differed between the two groups. No gastrointestinal perforation was observed (Tables 2, 3; details in Table 4).

Other than two nasal traumas appearing in the NHFOV group, four and two preterm infants were shown to have intestinal dilation in the NHFOV and NCPAP groups, respectively, and the intestinal dilation was alleviated after anal exhaust and artificial bowel movements. Seven cases of IVH grades 1/2 were observed before extubation. Of them, occipital hemorrhage appeared in one infant in the NHFOV group after extubation.

## Subgroup Analyses

In subgroup analyses, the reintubation rates did not show significant differences between the NHFOV and NCPAP groups at 32 to $36^{+6}$ weeks' gestational age (4:53 vs 10:48; 95% CI, 0.11-1.23; *P* = .094). However, in the preterm infants at ≤ 32 weeks' gestational age, the reintubation rates were significantly lower in the NHFOV group than in the NCPAP group (12:34 vs 25:20; 95% CI, 0.12-0.68; *P* = .004). On the other hand, NHFOV decreased the $P_{CO_2}$ levels within 6 h after extubation in both the subgroup of preterm infants with gestational age between 32 and $36^{+6}$ weeks (49.8 ± 6.9 vs 56.0 ± 8.6; 95% CI, −10.05 to −4.26; *P* = < .001) and the subgroup of preterm infants at gestational age ≤ 32 weeks (49.3 ± 6.5 vs 56.9 ± 11.6; 95% CI, −11.55 to −3.75; *P* = < .001) (Table 2).

To further assess the effects of the diagnoses of RDS and/or ARDS on reintubation, reintubation rates were compared in preterm infants in the NHFOV and NCPAP groups and who were diagnosed with RDS and/

**TABLE 2 ]** Primary Outcomes

| Primary Outcome | NHFOV (n = 103) | NCPAP (n = 103) | OR/MD | 95% CI | *P* Value |
|---|---|---|---|---|---|
| Reintubation (yes) | 16 (15.5) | 35 (34.0) | 0.35 | 0.18 to 0.70 | .002 |
| 32-$36^{+6}$, No. (total, %) | 4 (57, 7.0) | 10 (58, 17.2) | 0.36 | 0.11 to 1.23 | .094 |
| ≤ 32 wk, No. (total, %) | 12 (46, 26.1) | 25 (45, 55.6) | 0.28 | 0.12 to 0.68 | .004 |
| $P_{CO_2}$, 6 h after extubation, cm $H_2O$ | 49.6 ± 8.7 | 56.9 ± 9.9 | −7.15 | −9.95 to −4.80 | < .001 |
| 32-$36^{+6}$ | 49.8 ± 6.9 | 56.0 ± 8.6 | −7.37 | −10.05 to −4.26 | < .001 |
| ≤ 32 wk | 49.3 ± 6.5 | 56.9 ± 11.6 | −7.65 | −11.55 to −3.75 | < .001 |

MD = mean difference. See Table 1 legend for expansion of other abbreviations.

**TABLE 3 ]** Secondary Outcomes

| Secondary Outcome | NHFOV (n = 103) | NCPAP (n = 103) | OR/MD | 95% CI | *P* Value |
|---|---|---|---|---|---|
| IVH (yes), No. (%) | 12 (11.7) | 13 (12.6) | 0.91 | 0.40 to 2.11 | .831 |
| PDA (yes), No. (%) | 48 (46.6) | 42 (40.8) | 1.27 | 0.73 to 2.20 | .399 |
| ROP (yes), No. (%) | 6 (5.8) | 5 (4.9) | 1.21 | 0.36 to 4.11 | .757 |
| BPD (yes), No. (%) | 3 (2.9) | 6 (5.9) | 0.49 | 0.12 to 1.99 | .498 |
| NEC (yes), No. (%) | 14 (13.6) | 10 (9.7) | 1.46 | 0.62 to 3.46 | .385 |
| Hospital length of stay, d | 22.0 ± 14.3 | 27.6 ± 17.1 | −5.60 | −9.92 to −1.27 | .011 |
| Death (yes), No. (%) | 4 (3.9) | 6 (5.9) | 0.65 | 0.18 to 2.39 | .540 |
| Air leak (yes), No. (%) | 1 (1.0) | 0 (0) | 3.03 | 0.12 to 73.50 | .500 |

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity. See Table 1 and 2 legends for expansion of other abbreviations.

or ARDS. Compared with NCPAP, NHFOV could not significantly reduce the reintubation rate in preterm infants diagnosed with RDS (6:54 vs 14:53; 95% CI, 0.15-1.18; $P = .092$). However, NHFOV significantly reduced the reintubation rate in preterm infants diagnosed with ARDS and/or RDS (10:33 vs 21:15; 95% CI, 0.08-0.57; $P = .002$), and those diagnosed only with ARDS (8:26 vs 10:9; 95% CI, 0.08-0.92; $P = .032$) (Table 5).

To further assess the effects of RDS and/or ARDS and gestational age on the rate of reintubation, a test of diagnosis-by-gestational age subgroup interaction was also conducted, and no interaction was observed ($\chi^2 = 0.157$; 95% CI, 0.43-1.76; $P = .692$).

## Discussion

In this single-center, randomized controlled trial, we aimed to decrease the incidence of endotracheal

**TABLE 4 ]** Subgroup Analyses of Secondary Outcomes

| Secondary Outcome | NHFOV (n = 103) | NCPAP (n = 103) | OR/MD | 95% CI | *P* Value |
|---|---|---|---|---|---|
| IVH (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ [a] | 10 (17.5) | 7 (12.1) | 1.55 | 0.64 to 3.74 | .330 |
| ≤ 32 | 2 (4.3) | 6 (13.3) | 0.30 | 0.06 to 1.38 | .120 |
| PDA (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ | 29 (50.9) | 23 (40.4) | 1.58 | 0.75 to 3.30 | .220 |
| ≤ 32 | 19 (41.3) | 19 (42.2) | 1.00 | 0.71 to 1.41 | 1.000 |
| ROP (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ | 3 (5.3) | 4 (6.9) | 0.75 | 0.18 to 3.19 | .700 |
| ≤ 32 | 3 (6.5) | 1 (2.2) | 3.07 | 0.33 to 28.37 | .320 |
| BPD (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ | 2 (3.5) | 4 (6.9) | 0.49 | 0.09 to 2.57 | .400 |
| ≤ 32 | 1 (2.2) | 2 (4.4) | 0.48 | 0.04 to 5.08 | .540 |
| NEC (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ | 11 (19.3) | 5 (8.6) | 2.53 | 0.95 to 6.76 | .060 |
| ≤ 32 | 3 (6.5) | 5 (11.1) | 0.56 | 0.14 to 2.19 | .400 |
| Hospital stay, d | | | | | |
| $32\text{-}36^{+6}$ | 20.4 ± 11.3 | 27.3 ± 16.4 | −6.89 | −12.08 to −1.70 | .010 |
| ≤ 32 | 24.5 ± 13.0 | 27.3 ± 16.9 | −2.79 | −9.06 to 3.48 | .379 |
| Death (yes), No. (%) | | | | | |
| $32\text{-}36^{+6}$ | 4 (7.0) | 5 (8.6) | 0.80 | 0.23 to 2.82 | .730 |
| ≤ 32 | 0 (0) | 1 (2.2) | 0.32 | 0.01 to 7.63 | .480 |

See Table 1, 2, and 3 legends for expansion of abbreviations.
[a]Subgroups given as gestational age 32 to $36^{+6}$ wk ($32\text{-}36^{+6}$) and gestational age ≤ 32 wk (≤ 32).

**TABLE 5 ]** Comparison of Reintubation Rates in Preterm Infants in NHFOV and NCPAP Groups and Diagnosed With RDS and/or ARDS

| Diagnosis | NHFOV | NCPAP | 95% CI | *P* Value |
|---|---|---|---|---|
| RDS (yes), No. (total, %) | 6 (60, 10.0) | 14 (67, 20.9) | 0.15-1.18 | .092 |
| RDS and ARDS (yes), No. (total, %) | 2 (9, 22.2) | 11 (17, 64.7) | 0.02-1.00 | .097 |
| Only ARDS (yes), No. (total, %) | 8 (34, 23.5) | 10 (19, 52.6) | 0.08-0.92 | .032 |
| ARDS and/or RDS (yes), No. (total, %) | 10 (43, 23.3) | 21 (36, 58.3) | 0.08-0.57 | .002 |

RDS = respiratory distress syndrome. See Table 1 legend for expansion of other abbreviations.

reintubation and $P_{CO_2}$ levels in preterm infants by comparing NHFOV with NCPAP as postextubation respiratory support modes. As a result, we found that NHFOV did significantly reduce the need for endotracheal ventilation as compared with NCPAP, especially in the subgroup at ≤ 32 weeks' gestational age. A similar effect also appeared on the clearance of $P_{CO_2}$, including both subgroups.

We also show that the effects of NHFOV and NCPAP on reintubation were associated with the causes of respiratory failure. Compared with NCPAP, NHFOV significantly reduced the reintubation rate in preterm infants with ARDS. To our knowledge, this is the first study comparing NHFOV with NCPAP as postextubation respiratory support modes in preterm infants with neonatal ARDS. The results suggest that NHFOV can be superior to NCPAP in preterm neonates.

Up to now, several studies have compared the effects of NHFOV and NCPAP on reintubation in preterm infants, and the results were encouraging. In 1998, van der Hoeven et al[13] applied NHFOV (amplitude, 35 cm $H_2O$; MAP, 7 cm $H_2O$; and frequency, 10 Hz) in 21 preterm and term infants for respiratory insufficiency. The result indicated that NHFOV significantly decreased the $P_{CO_2}$ level compared with NCPAP and could be used to decrease the need for invasive ventilation. Our previous randomized controlled study compared the effects of NHFOV with NCPAP on the need for invasive ventilation as primary respiratory support mode in preterm infants with moderate-severe RDS, and the results indicated that NHFOV significantly reduced the need for invasive ventilation.[17] In the present study, the data show that NHFOV reduced the need for endotracheal ventilation compared with NCPAP, especially in the subgroup at a gestational age ≤ 32 weeks; this was consistent with another study[28] performed in China, in which NHFOV was applied as a rescue treatment after the failure of other noninvasive ventilation modes, or was prophylactically used in neonates at high risk of reintubation. In contrast, Klotz et al[29] did a randomized controlled cross-over trial in 26 preterm infants, and the result showed no difference in failure of noninvasive respiratory support ($P = .051$) and clearance of $P_{CO_2}$ ($P = .33$).

A probable reason for the differences was the cause of respiratory failure. In the study by Klotz et al,[29] the included preterm infants were diagnosed with RDS, and their results were consistent with ours in preterm infants diagnosed with RDS. As far as ARDS and/or RDS were concerned, NHFOV significantly reduced the intubation rate. A reasonable explanation is that RDS is primarily restrictive in the acute phase, and the high-frequency oscillation combined with CPAP does not therefore bring any benefit. However, ARDS is both restrictive and obstructive in the acute phase, due to the nature of ARDS; NHFOV is therefore able to improve oxygenation.

NHFOV has been reported to have the potential to reduce airway resistance, the work of breathing,[30] and lung inflammatory markers,[31] and to improve oxygenation, lung compliance,[29] and alveolar development.[32,33] However, the exact mechanism by which NHFOV improves efficacy has not been fully explained. Thus, a better understanding of its exact actions is needed in further studies. One of the possible mechanisms by which NHFOV works is to decrease mean levels of $P_{CO_2}$.[20] The study by Colaizy et al[16] in 14 very preterm infants (median gestational age, 27 weeks; median weight at study, 1,605 g) indicated that, compared with NCPAP (pressure, 4-7 cm $H_2O$), NHFOV (the same pressure as with NCPAP) significantly reduced the level of $P_{CO_2}$ (45 vs 50; $P = .01$) and increased the pH (7.40 vs 7.37; $P = .04$) after 2 h. Another retrospective study[10] included 79 neonates in four centers, and the results showed that, compared with another noninvasive mode, NHFOV significantly reduced the mean number of apneas, bradycardias, and desaturations (over 6 h) (3.2 ± 0.4 vs 1.2 ± 0.3; $P < .001$), $F_{IO_2}$ (48 ± 3 vs 40 ± 2; $P < .001$), and $P_{CO_2}$

levels (74 ± 6 vs 62 ± 4 mm Hg; $P = .025$). Furthermore, Czernik et al[9] also reported an observational study of 20 mechanically ventilated neonates at high risk for extubation failure, and the results showed that NHFOV could be successfully used to wean preterm infants from invasive ventilation and $P_{CO_2}$ significantly declined at 32 h from 59.8 to 50.7 mm Hg ($P < .01$). But, $P_{CO_2}$ returned again to preextubation levels after termination of NHFOV.

Time-dependent effects should be one of the causes inducing inconsistent $P_{CO_2}$ levels,[9] and 4 h might be not enough time to reduce the $P_{CO_2}$ levels.[29] Otherwise, another cause might be the amplitudes given. In actuality, the amplitudes were different among these trials. The amplitude in the study by Klotz et al was "clearly visible oscillations of the chest," and it was 20 cm $H_2O$ in the study by Czernik et al. But in the present study, the set amplitude was 35 cm $H_2O$, which was consistent with the study by van der Hoeven et al.[13]

Similar to NCPAP and HFOV, NHFOV might also induce some side effects. Fischer et al[26] demonstrated that abdominal distension, upper airway obstruction due to secretions, and highly viscous secretions were the most common side effects of NHFOV. Other side effects included leakage around the prongs, strong agitation, pneumothorax, and ventilator dysfunction. Other than these, Czernik et al[9] also reported air trapping and necrotizing enterocolitis. No feeding intolerance or skin lesions were observed in association with NHFOV therapy. In the present study, nasal trauma and intestinal dilation were observed in the NHFOV group, which was consistent with the report by Fischer et al.[34]

The major limitations of the present study were as follows: (1) few preterm infants below 28 weeks' gestational age; and (2) single-center study in Chinese newborns. These limitations might induce potential bias, including restricted application scope. The problems could be overcome in additional studies. To this end we have recently organized two international, multicenter, randomized controlled trials regarding the comparison of NCPAP and/or NIPPV and NHFOV as primary/postextubation respiratory support modes in preterm infants (NCT03181958 and NCT03099694).

In summary, among preterm ventilated infants, NHFOV can be superior to NCPAP with respect to avoiding reintubation as a postextubation respiratory support strategy in early life, especially in very preterm infants and those infants diagnosed with ARDS.

## Acknowledgments

**Author contributions:** All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. L. C. conceptualized and designed the study, performed the clinical trial, drafted the initial manuscript, and reviewed the manuscript. L. W. designed the data collection instruments, coordinated and supervised data collection, and reviewed the manuscript. J. M. performed the clinical trial, drafted the initial manuscript, and reviewed the manuscript. Z. F. carried out the initial analyses and reviewed the manuscript. J. L. conceptualized and designed the study, enforced the randomization, and reviewed the manuscript. Y. S. conceptualized and designed the study and critically reviewed the manuscript for important intellectual content.

**Financial/nonfinancial disclosures:** None declared.

**Role of sponsors:** The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

**Other contributions:** The authors thank the 206 preterm babies and their parents for supporting this study. The authors also thank Zhou Ping and Chandler Jobs (Chongqing Medical University, China) for valuable suggestions that greatly improved the written presentation of this article. Additionally, the authors thank the Social Livelihood Program of Chongqing Science and Technology Commission, China (No. cstc2018jscx-msybX0040).

**Additional information:** The e-Appendix can be found in the Supplemental Materials section of the online article.

## References

1. Stroustrup A, Trasande L. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993-2006. *Pediatrics*. 2010;126(2):291-297.
2. Donn SM, Sinha SK. Minimising ventilator induced lung injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(3):F226-F230.
3. Natarajan G, Pappas A, Shankaran S, et al. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev*. 2012;88(7):509-515.
4. Terragni P, Ranieri VM, Brazzi L. Novel approaches to minimize ventilator-induced lung injury. *Curr Opin Crit Care*. 2015;21(1):20-25.
5. Davis PG, Schmidt B, Roberts RS, et al. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr*. 2010;156(3):382-387.
6. Stefanescu BM, Murphy WP, Hansell BJ, Fuloria M, Morgan TM, Aschner JL. A randomized controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. *Pediatrics*. 2003;112(5):1031-1038.
7. Cherif A, Hachani C, Khrouf N. Risk factors of the failure of surfactant treatment by transient intubation during nasal continuous positive airway pressure in preterm infants. *Am J Perinatol*. 2008;25(10):647-652.
8. De Luca D, Dell'Orto V. Non-invasive high-frequency oscillatory ventilation in neonates: review of physiology, biology and clinical data. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(6):F565-F570.
9. Czernik C, Schmalisch G, Bührer C, Proquitté H. Weaning of neonates from mechanical ventilation by use of nasopharyngeal high-frequency oscillatory ventilation: a preliminary study. *J Matern Fetal Neonatal Med*. 2012;25(4):374-378.
10. Mukerji A, Singh B, Helou SE, et al. Use of noninvasive high-frequency ventilation in the neonatal intensive care unit: a retrospective review. *Am J Perinatol*. 2015;30(2):171-176.
11. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute

Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439.

12. De Luca D, van Kaam AH, Tingay DG, et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. *Lancet Respir Med*. 2017;5(8):657-666.
13. van der Hoeven M, Brouwer E, Blanco CE. Nasal high frequency ventilation in neonates with moderate respiratory insufficiency. *Arch Dis Child Fetal Neonatal Ed*. 1998;79(1):61-63.
14. De Luca D, Carnielli VP, Conti G, Piastra M. Noninvasive high frequency oscillatory ventilation through nasal prongs: bench evaluation of efficacy and mechanics. *Intensive Care Med*. 2010;36(12):2094-2100.
15. Hoehn T, Krause MF. Effective elimination of carbon dioxide by nasopharyngeal high-frequency ventilation. *Respir Med*. 2010;94(11):1132-1134.
16. Colaizy TT, Younis UM, Bell EF, Klein JM. Nasal high frequency ventilation for premature infants. *Acta Paediatr*. 2008;97(11):1518-1522.
17. Zhu XW, Zhao JN, Tang SF, Yan J, Shi Y. Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: a preliminary report. *Pediatr Pulmonol*. 2017;52(8):1038-1042.
18. Jasani B, Nanavati R, Kabra N, Rajdeo S, Bhandari V. Comparison of non-synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as post-extubation respiratory support in preterm infants with respiratory distress syndrome: a randomized controlled trial. *J Matern Fetal Neonatal Med*. 2016;29(10):1546-1551.
19. De Luca D, Piastra M, Pietrini D, Conti G. Effect of amplitude and inspiratory time in a bench model of non-invasive HFOV through nasal prongs. *Pediatr Pulmonol*. 2012;47(10):1012-1018.
20. Mukerji A, Finelli M, Belik J. Nasal high-frequency oscillation for lung carbon dioxide clearance in the newborn. *Neonatology*. 2013;103(3):161-165.
21. De Luca D, Costa R, Visconti F, Piastra M, Conti G. Oscillation transmission and volume delivery during face mask-delivered HFOV in infants: bench and in vivo study. *Pediatr Pulmonol*. 2016;51(7):705-712.
22. De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. *Am J Respir Crit Care Med*. 2006;174(6):639-645.
23. Kieran EA, Twomey AR, Molloy EJ, Murphy JF, O'Donnell CP. Randomized trial of prongs or mask for nasal continuous positive airway pressure in preterm infants. *Pediatrics*. 2012;130(5):e1170-e1176.
24. Chen L, Wang L, Li J, Wang N, Shi Y. Noninvasive ventilation for preterm twin neonates with respiratory distress syndrome: a randomized controlled trial. *Sci Rep*. 2015;5:14483.
25. 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:CD003212.
26. Fischer HS, Bohlin K, Bührer C, et al. Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. *Eur J Pediatr*. 2015;174(4):465-471.
27. Wang C, Chen L, Wang L, Wang N, Wu T, Shi Y. Nasal intermittent positive pressure ventilation versus after extubation: a retrospective analysis. *Chongqing Med*. 2013;36:4408-4411.
28. Wang CH, Shi LP, Ma XL, Lin HJ, Xu YP, Du LZ. Use of noninvasive high frequency oscillatory ventilation in very low birth weight infants. *Zhonghua Er Ke Za Zhi*. 2017;55(3):177-181.
29. Klotz D, Schneider H, Schumann S, Mayer B, Fuchs H. Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomized controlled cross-over trial. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(4):F1-F5.
30. Mukerji A, Dunn M. High-frequency ventilation as a mode of noninvasive respiratory support. *Clin Perinatol*. 2016;43(4):725-740.
31. Yoder BA, Siler-Khodr T, Winter VT, Coalson JJ. High-frequency oscillatory ventilation: effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. *Am J Respir Crit Care Med*. 2000;162(5):1867-1876.
32. Null DM, Alvord J, Leavitt W, et al. High-frequency nasal ventilation for 21 d maintains gas exchange with lower respiratory pressures and promotes alveolarization in preterm lambs. *Pediatr Res*. 2014;75(4):507-516.
33. Rehan VK, Fong J, Lee R, et al. Mechanism of reduced lung injury by high frequency nasal ventilation in a preterm lamb model of neonatal chronic lung disease. *Pediatr Res*. 2011;70(5):462-466.
34. Fischer C, Bertelle V, Hohlfeld J, Forcada-Guex M, Stadelmann-Diaw C, Tolsa JF. Nasal trauma due to continuous positive airway pressure in neonates. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(6):F447-F451.