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ORIGINAL RESEARCH

The Effects of HFOV-VG vs HFOV on Bronchopulmonary Dysplasia and Neurobehavioral Development in Preterm Infants with Perinatal Acute Respiratory Distress Syndrome

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Objective: This study aimed to explore whether high-frequency oscillatory ventilation with volume-guarantee (HFOV-VG) strategy could reduce the incidence of bronchopulmonary dysplasia (BPD) and improve poor neurological prognosis in premature infants with perinatal acute respiratory distress syndrome (NARDS) compared with high-frequency oscillatory ventilation (HFOV) alone.

Methods: This retrospective single-center study conducted in the neonatal intensive care unit (NICU) from January 2016 and December 2023. One hundred and seventy-two premature infants (32 weeks ≤ gestational age < 37 weeks) with NARDS were enrolled. Infants were categorized into two groups based on ventilation strategy: HFOV-VG (n = 70) and HFOV (n = 102). The demographic data, perinatal factors, primary and secondary outcomes were compared. Univariate and multivariate logistic regression analyses were performed to assess the association between the ventilation strategy and primary outcomes.

Results: The invasive mechanical ventilation duration and incidence of BPD in HFOV-VG group were lower than those in HFOV group. There were no significant differences in complication, and the scores of neurobehavioral development between the two groups of children who were followed up until correct age of 6 months. The multivariate logistic regression analysis identified that the ventilation strategy of HFOV-VG was an independent protective factor of BPD. However, HFOV-VG was not associated with a statistically significant improvement in short-term neurodevelopmental outcomes. Subgroup analysis showed that there were no significant interactions in any of the subgroups except for birth weight subgroup. The association between HFOV-VG mode and the incidence of BPD was more pronounced in neonates with birth weight < 2500g.

Conclusion: The ventilation strategy of HFOV-VG was a promising lung protective mode for premature infants with perinatal ARDS, which can shorten mechanical ventilation duration and may reduce the incidence of BPD. However, it did not seem to be superior to HFOV in improving short-term neurodevelopmental outcomes.

Keywords: acute respiratory distress syndrome, bronchopulmonary dysplasia, high frequency oscillatory ventilation, high-frequency oscillatory ventilation with volume-guarantee, neurobehavioral development

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Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory illness in neonates, triggered by diverse etiologies. It is pathologically characterized by diffuse pulmonary exudation, decreased compliance, hyaline membrane formation, and alveolar collapse. Clinically, it manifests as severe hypoxemia, respiratory distress, and reduced lung compliance, with a mortality as high as 17% to 24%.[1] Perinatal risk factors can significantly increase the incidence of ARDS. A prospective, multicenter, cross-sectional study reported that the cumulative incidences of ARDS were 94.1% within three days after birth.[2]

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Therefore, it is important to explore effective treatments for perinatal ARDS (onset time < 72 hours after birth) (NARDS) to reduce mortality and improve prognosis.

Mechanical ventilation is an essential supportive therapy for neonatal ARDS but paradoxically represents a significant risk factor for ventilator-induced lung injury (VILI). The choice of ventilation strategy is related to the occurrence and development of bronchopulmonary dysplasia (BPD) and neonatal white matter injury.[3] Optimizing ventilator modalities that align with the unique pathophysiological characteristics of neonatal ARDS is therefore a critical challenge for neonatologists. High-frequency oscillatory ventilation (HFOV) has been widely utilized in neonatal ARDS. However, conventional HFOV lacks integrated flow sensors, making it impossible to monitor the flow rate and tidal volume of each oscillation. Meanwhile, the actual tidal volume under HFOV is larger than the anatomical dead space volume, which may lead to adverse outcomes such as hyperventilation, hyperoxia brain injury, pneumothorax, and ventilator-associated lung injury. Therefore, in order to control tidal volume, a new ventilation strategy has emerged, namely high-frequency oscillatory ventilation with volume-guarantee (HFOV-VG), which has become a research hotspot in the field of neonatal respiratory support in recent years. Animal studies have reported that HFOV-VG strategy can optimize gas exchange efficiency and reduce ventilator lung injury.[4,5] However, there is very little research on HFOV-VG in neonates, and it is still unclear whether it can prevent lung injury in the treatment of ARDS. In addition, studies have reported that VG can reduce the incidence of intracranial hemorrhage in premature infants, and premature infants treated with HFOV have a significantly reduced risk of cerebral palsy and delayed mental development at 18 months of age.[6,7] All of these suggested that the ventilation mode may affect the neurobehavioral development of infants, but there is no research focusing on the effects of HFOV-VG mode on the neurobehavioral development of ARDS infants. Therefore, we conducted this retrospective study to compare the effects of HFOV-VG versus HFOV on the incidence of BPD and neurobehavioral development at 6 months corrected age in premature infants with NARDS. The primary research question was: Does HFOV-VG, compared to HFOV alone, reduce the incidence of BPD and improve neurobehavioral development scores in preterm infants with NARDS? We hypothesized that: (1) HFOV-VG would be associated with a lower incidence of BPD. (2) HFOV-VG would be associated with higher neurobehavioral development scores at 6 months corrected age.

Materials and Methods

Patient Selection

This retrospective study was conducted in the Neonatal Intensive Care Unit (NICU) at the First Hospital Affiliated to Army Medical University, China, from 1 January 2016 to 31 December 2023. Ultimately, 172 middle-late premature infants[8] with NARDS who received HFOV-VG or HFOV were enrolled.

Inclusion Criteria

(1) Gestational age between 32 and 36^{+6} weeks; (2) onset within 72 hours after birth; (3) diagnosed as ARDS according to Montreux criteria; (4) moderate-to-severe ARDS; (5) HFOV or HFOV-VG ventilation.

Exclusion Criteria

(1) Neonates with malformation of the lung, such as congenital pulmonary dysplasia, pulmonary sequestration, congenital diaphragmatic hernia; (2) neonates with pulmonary edema caused by congenital heart disease; (3) primary pulmonary surfactant deficiency; (4) neonates with crossover between HFOV and HFOV-VG; (5) death.

Intervention

Indications for invasive ventilation included respiratory failure: hypoxemia, $PaO_2 < 50$ mmHg under auxiliary oxygen supply or non-invasive ventilation; respiratory acidosis, arterial blood gas pH < 7.2 and arterial carbon dioxide partial pressure ($PaCO_2$) > 60 mmHg; severe apnea; fraction of inspired oxygen (FiO_2) > 40%.[9] In this study, HFOV or HFOV-VG was mainly used for treatment rather than rescue.

Study Exposure and Ventilation Strategies

The exposure for this study was the presence of VG. Infants received ventilation with fabian ventilators (software version: HFO 3.4.0). Ventilator parameters were applied according to a standardized protocol. HFOV-VG Ventilation Strategy: VThf was set at 1.5–2.5 mL/kg with an oscillatory frequency of 10–15 Hz. Initial MAP ranged from 6 to 8 cmH_2O. Amplitude (ΔP) was initiated at 15–20 cmH_2O, or dynamically adjusted by observing thoracoabdominal oscillation extending to the pelvic region. FiO_2 was 0.25–1.00 to maintain percutaneous oxygen saturation (SpO_2) at 90%–95%, with a fixed inspiratory-to-expiratory ratio (I:E) of 1:2. Lung Recruitment Maneuver: MAP was increased by 1–2 cmH_2O every 2–3 minutes while concurrently reducing FiO_2 to sustain target SpO_2. MAP escalation ceased when any criterion was met (defining alveolar opening pressure): ① $FiO_2 \leq 0.25$; ② Absence of further SpO_2 improvement; ③ Signs of pulmonary hyperinflation. MAP was decreased by 1–2 cmH_2O every 2–3 minutes until SpO_2 declined (defining closing pressure). Lung reopening: MAP restored to opening pressure for 2–3 minutes. Final MAP set at closing pressure + 2 cmH_2O. Parameter Optimization: Arterial blood gas analysis at 30 minutes guided VThf adjustments in 0.1–0.2 mL/kg. Amplitude ceiling was established at 115%–120% of the mean ΔP required to achieve target VThf.[10] HFOV Ventilation Strategy: Oscillatory frequency 10–15 Hz, amplitude 20–40 cmH_2O, initial MAP 10–16 cmH_2O, I:E = 1:2, and FiO_2: 0.25–1.00 (targeting SpO_2 > 90%–95%). All parameters were dynamically adjusted based on clinical status, arterial blood gases, and guideline recommendations.[11] Maintaining arterial blood gas in ARDS infants within the following range: pH 7.25–7.45, PaO_2: 50–80mmHg, $PaCO_2$: 35–55mmHg, SpO_2: 90–95%.

Extubation criteria are as follows: hemodynamic stability, $PaCO_2$ < 55 mmHg, MAP < 10 cmH2O, $FiO_2 \leq 30\%$, adequate spontaneous breathing without any clinical or radiological respiratory distress symptoms.[12] Some infants were extubated in HFOV mode, and others were transferred to conventional ventilation 1–2 days before extubation.

Study Outcomes

The data for all the study patients were obtained from the electronic medical records. BPD and neurobehavioral development at correct age of 6 months (the data at 12 months corrected age was incomplete) were the primary outcomes for this study. We use Gesell developmental scale to assess neurobehavioral development. The secondary outcomes were duration of invasive ventilation and non-invasive ventilation, complications during hospitalization, such as air leakage, retinopathy of prematurity (ROP) ≥ 2nd, necrotizing enterocolitis (NEC) ≥ 2nd, and intraventricular hemorrhage (IVH) ≥ 3rd stage, and duration of hospitalization.

Covariates

Covariates were selected based on the existing literature in which an association between those indicators and the incidence of BPD and neurobehavioral development at correct age of 6 months in ARDS was reported.[13–16]

Participant information at baseline including: (1) perinatal factors: maternal age, premature rupture of membranes ≥ 18 h, meconium-stained amniotic fluid (MSAF), prenatal glucocorticoid, etc; (2) demographics: gestational age, birth weight, gender, mode of delivery, 1 and 5-min Apgar score, oxygenation index (OI), etc; (3) triggers of ARDS: early-onset sepsis, meconium aspiration syndrome (MAS), pulmonary hemorrhage, pneumonia and perinatal asphyxia, aspiration of blood.

Definition of the Important Diagnoses and Concepts

Neonates diagnosed with ARDS according to the Montreux criteria: (1) acute respiratory distress with clear or suspected clinical injury, oxygenation disorders accompanied by decreased residual air volume, requiring positive pressure ventilation to facilitate lung recruitment; (2) exclusion of respiratory distress resulting from neonatal respiratory distress syndrome (NRDS), transient tachypnoea of the neonate, or congenital anomalies; (3) Pulmonary imaging shows that transparency of bilateral diffuse irregular decreased which cannot be explained by other reasons; (4) respiratory failure caused by pulmonary edema cannot be fully explained by heart failure. The severity of ARDS was defined as follows:[17] mild $4 \leq OI < 8$, moderate $8 \leq OI < 16$ or 7.5, severe $OI \geq 16$. $OI = (FiO_2 \times MAP \times 100) / PaO_2$.

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The diagnosis of BPD refers to the 2001 NICHD criteria.[18] The diagnosis of ROP, NEC and IVH can be referred to the fifth edition of Practical Pediatrics.[19] Collect the results of the Gesell Developmental Scale at correct age of 6 months, which includes five functional areas: gross motor, fine motor, adaptive behavior, language, and personal social behavior. Use normal behavior patterns as the standard to identify observed behavior patterns, represented by age. Then, compare with actual age to calculate the development quotient (DQ). $DQ \geq 85$ is considered normal for the nervous system, $75 \leq DQ < 85$ is the critical level of nervous system damage, and $DQ < 75$ is considered nervous system damage.

Statistical Analysis

The Kolmogorov–Smirnov test was performed to assess the normality of the variable distributions. Variables following a normal distribution were expressed as mean (standard deviation), while those not normally distributed were expressed as median (interquartile range). Categorical variables were summarized as counts (percentage, %). Continuous variables with a normal distribution were analyzed using Student's *t*-test, whereas those with a non-normal distribution were evaluated using the Kruskal–Wallis test. Comparisons of categorical variables were conducted using the Chi-Squared test.

To explore the association between different ventilation modes (HFOV and HFOV-VG) and outcomes such as BPD and neurobehavioral development, univariate and multivariable logistic regression models were employed among neonates with NARDS. The selection of covariates in this study was guided by theoretical frameworks and literature on factors associated with infants with NARDS, prioritizing variables relevant to both exposure and outcome.[13–16] Additional considerations included controlling for confounding factors, aligning with study objectives, balancing sample size, and ensuring clinical significance to enhance the robustness and interpretability of the results. The modeling procedure is as follows: Initially, variables with $p < 0.1$ identified from the univariate logistics regression analysis are selected for multivariate logistics regression analysis. Subsequently, variables with $p < 0.5$ and $p > 0.5$ will emerge in the results. Then, the process of multivariate logistics regression analysis is repeated, and variables with $p > 0.5$ are successively removed. The changes in Exp (B) values of the target variable (ventilation mode) are observed after the deletion of each variable. If the Exp (B) value exhibits a deviation of more than 10% following the removal of a specific variable, the variable will be retained; otherwise, it will be deleted.

We fitted three statistical models. For BPD, Model 1 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male); Model 2 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male), surfactant treatment; Model 3 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male), surfactant treatment, meconium-stained amniotic fluid and EOS. For the neurobehavioral development, Model 1 adjusted for age at admission, gender (male), lactate at admission, maternal age and OI. Model 2 adjusted for age at admission, gender (male), lactate at admission, maternal age, OI, surfactant treatment and duration of non-invasive ventilation. Model 3 adjusted for age at admission, gender (male), lactate at admission, maternal age, OI, surfactant treatment, duration of non-invasive ventilation, meconium-stained amniotic fluid and perinatal asphyxia.

We further stratified the analysis of significant covariates to consider potential impacts. In this study, we stratified analysis according to gestational age, birth weight, gender, PROM, prenatal glucocorticoid. All statistical analyses were performed using SPSS (version 27.0) or GraphPad Prism (version 10.0.3). A twosided $p < 0.05$ was considered to be statistically significant.

Results

Clinical Characteristics of Neonates with NARDS

Between 1 Jan 2016 and 31 Dec 2023, a total of 242 ARDS infants who met the inclusion criteria were admitted to the NICU, the First Affiliated Hospital of the Army Medical University. According to the exclusion criteria, 172 infants were ultimately included (102 were assigned to HFOV group and 70 to HFOV-VG group) (Figure 1). Among them, 18 infants (10.47%) developed BPD. Compared with the HFOV group, the HFOV-VG group had shorter invasive ventilation and hospitalization time, and lower incidence of BPD ($p < 0.05$). In addition, there were differences in PROM, EOS and pneumonia between the two groups ($p < 0.05$) (Table 1). The distribution of BPD and neurobehavioral development among NARDS infants with different ventilation strategies were showed in Figure 2.

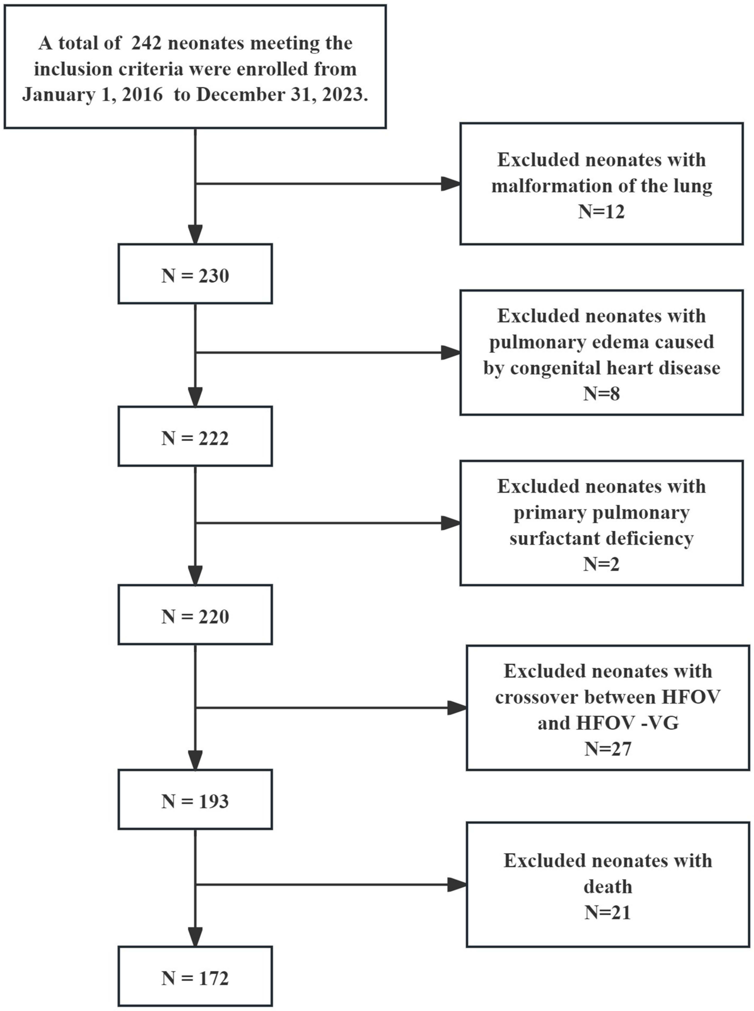


Figure 1 Flow chart for patients selection.

Association Between Ventilator Mode and Primary Outcomes

Logistic regression analysis was used to examine the relationship between the ventilator mode and primary outcomes. In univariate analysis, we found that ventilation mode was associated with lower risk of BPD (OR = 0.260, 95% CI: 0.072–0.934, p = 0.039) (Table 2), but not with the neurobehavioral development (Table 3). Moreover, gestational age, PROM, prenatal glucocorticoid, MSAF and EOS were also associated with BPD (Table 2).

Table 1 Baseline Characteristics of Neonates with NARDS in HFOV and HFOV-VG Groups

Variable	**Overall (n = 172)**	**HFOV (n = 102)**	**HFOV-VG (n = 70)**	***p***
Demographic and perinatal data of neonates				
Gestational age, days	35.00(33.85, 36.00)	35.00(33.82, 36.14)	35.07(33.96, 36.00)	0.959
Gender (male) (n%)	102(59.30)	60(58.82)	42(60.00)	0.877
Birth weight, g	2305.00(1830.00, 2752.50)	2295.00(1777.50, 2765.00)	2365.00(1907.50, 2737.50)	0.540
Maternal age, years	31.44 ± 4.36	31.71 ± 4.63	31.04 ± 3.93	0.314
Multiple births (n%)	39(22.67)	24(23.53)	15(21.43)	0.747
Vaginal birth (n%)	26(15.12)	14(13.73)	12(17.14)	0.539

(*Continued*)

Table 1 (Continued).

Variable	Overall (n = 172)	HFOV (n = 102)	HFOV-VG (n = 70)	*p*
Age at admission, h	0.33(0.29, 0.42)	0.33(0.29, 0.42)	0.34(0.30, 0.43)	0.760
Age at NARDS diagnosis, h	27.00(23.25, 32.00)	27.00(23.75, 32.00)	28.00(23.00, 32.00)	0.420
PROM (n%)	95(55.23)	74(72.55)	21(30.00)	<0.001
Prenatal glucocorticoid (n%)	52(30.23)	33(32.35)	19(27.14)	0.465
Postnatal glucocorticoid (n%)	9(5.23)	6(5.88)	3(4.29)	0.644
1' Apgar score	10.00(9.00, 10.00)	10.00(9.00, 10.00)	10.00(9.00, 10.00)	0.270
5' Apgar score	10.00(10.00, 10.00)	10.00(10.00, 10.00)	10.00(10.00, 10.00)	0.097
SGA (n%)	17(9.88)	11(10.78)	6(8.57)	0.633
MSAF (n%)	24(13.95)	13(12.75)	11(15.71)	0.581
OI	16.67 ± 4.89	16.31 ± 4.92	17.19 ± 4.78	0.247
Lactate at admission, mmol/L	1.90(1.40, 2.60)	1.90(1.30, 2.90)	1.80(1.40, 2.20)	0.650
hsPDA (n%)	7(4.07)	5(4.90)	2(2.86)	0.505
Surfactant treatment (yes) (n%)	89(51.74)	50(49.02)	39(55.71)	0.388
Triggers of NARDS in HFOV and HFOV-VG groups				
EOS (n%)	62(36.05)	43(42.16)	19(27.14)	0.044
Pulmonary hemorrhage (n%)	28(16.28)	16(15.69)	12(17.14)	0.799
MAS (n%)	12(6.98)	7(6.86)	5(7.14)	0.944
Pneumonia (n%)	55(31.98)	26(25.49)	29(41.43)	0.028
Perinatal asphyxia (n%)	8(4.65)	6(5.88)	2(2.86)	0.355
Aspiration of blood (n%)	7(4.07)	4(3.92)	3(4.29)	0.905
Primary outcomes				
BPD (n%)	18(10.47)	15(14.71)	3(4.29)	0.028
The Gesell Developmental Scale (DQ < 75)				
Gross motor (n%)	7(4.07)	4(3.92)	3(4.29)	0.905
Fine motor (n%)	6(3.49)	4(3.92)	2(2.86)	0.709
Adaptive behavior (n%)	7(4.07)	5(4.90)	2(2.86)	0.505
Language (n%)	8(4.65)	6(5.88)	2(2.86)	0.355
Personal-social behavior (n%)	7(4.07)	5(4.90)	2(2.86)	0.505
Secondary outcomes				
Air leak (n%)	3(1.74)	2(1.96)	1(1.43)	0.793
IVH ≥ 3rd (n%)	6(3.49)	4(3.92)	2(2.86)	0.709
ROP (yes) ≥ 2nd (n%)	2(1.16)	2(1.96)	0(0.00)	0.239
NEC (yes) ≥ 2nd (n%)	14(8.14)	8(7.84)	6(8.57)	0.864
Duration of invasive ventilation, h	135.00(104.25, 169.00)	145.50(103.50, 183.25)	129.00(103.50, 147.25)	0.023
Ventilation free hours, h	85.00(71.00, 102.75)	87.00(71.75, 107.00)	79.00(67.50, 96.00)	0.071
Duration of hospitalization, days	16.50(13.00, 22.75)	18.00(14.00, 24.50)	15.00(13.00, 19.00)	0.024

Notes: The continuous variables of non-normal distribution were presented as median (quartile ranges), and normal distribution were presented as the mean value ± standard deviation. Differences in continuous variables were assessed for significance using *t*-test or Mann–Whitney *U*-tests. Categorical variables were presented as absolute numbers and percentages, and were compared using Chi-square test and Fisher's Exact test. $P < 0.05$ was considered significant.

Abbreviations: BPD, bronchopumonary dysplasia; EOS, early-onset sepsis; HFOV, high-frequency oscillatory ventilation; HFOV-VG, High-frequency oscillatory ventilation with volume-guaranteen; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; MAS, meconium aspiration syndrome; MSAF, meconium-stained amniotic fluid; NARDS, neonatal acute respiratory distress syndrome; NEC, necrotizing enterocolitis; OI, oxygenation index; PROM, premature rupture of membranes; ROP, retinopathy of prematurity; SGA, small for gestational age.

The confounding factors and ventilation strategy, identified through univariate screening ($p < 0.1$), would be utilized to construct models in multivariable logistic regression analysis to explore the independent association between the ventilator mode and BPD and neurobehavioral development. In Model 1, HFOV-VG mode was significantly negative

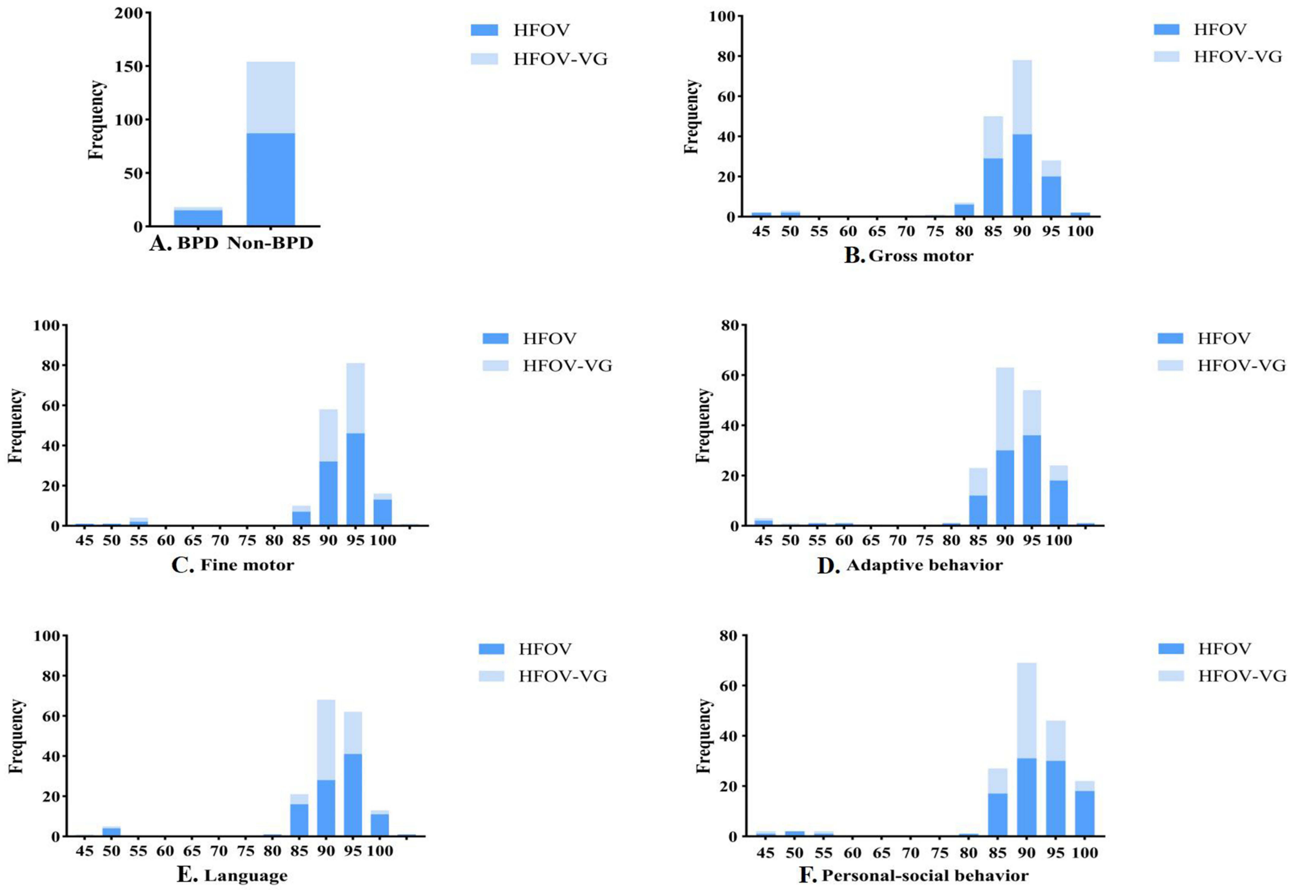


Figure 2 Histograms show the population distribution of BPD and The Gesell Developmental Scale with HFOV and HFOV-VG. (**A**) BPD; (**B**) Gross motor; (**C**) Fine motor; (**D**) Adaptive behavior; (**E**) Language; (**F**) Personal-social behavior.

with the occurrence of BPD (OR = 0.229, 95% CI: 0.062–0.843, *p* = 0.027). This negative association persisted in the minimally adjusted model (OR = 0.231, 95% CI: 0.063–0.852, *p* = 0.028). After full adjustment, the ventilation strategy of HFOV-VG remained negatively linked to the occurrence of BPD (OR = 0.143, 95% CI: 0.035–0.578, *p* = 0.006)

Table 2 Univariate Logistics Regression Analysis of the Association Between Ventilation Mode and BPD

Characteristic	**BPD**		**Characteristic**	**BPD**	
	OR (95% CI)	***p* value**		**OR (95% CI)**	***p* value**
Gestational age	1.075(1.010–1.145)	0.024	HsPDA	0.000(0.000–0.000)	0.999
Birth weight,	1.001(1.000–1.002)	0.068	Surfactant treatment	0.428(0.153–1.198)	0.106
Gender (male)	1.422(0.507–3.988)	0.503	EOS	0.090(0.012–0.691)	0.021
Maternal age	0.978(0.874–1.094)	0.695	MAS	1.800(0.362–8.948)	0.473
Multiple births	0.656(0.180–2.392)	0.523	Pneumonia	1.071(0.380–3.022)	0.896
Vaginal birth	2.436(0.787–7.536)	0.122	Pulmonary hemorrhage	2.191(0.713–6.731)	0.171
Age at admission	1.049(0.904–1.217)	0.530	Perinatal asphyxia	3.083(0.574–16.567)	0.189
Age at NARDS diagnosis	1.060(0.972–1.156)	0.190	Aspiration of blood	3.725(0.668–20.781)	0.134
PROM	4.625(1.287–16.622)	0.019	Air leak	0.000(0.000–0.000)	0.999
Prenatal glucocorticoid	0.119(0.015–0.918)	0.041	IVH ≥ 3rd	0.000(0.000–0.000)	0.999
Postnatal glucocorticoid	1.074(0.126–9.112)	0.948	ROP ≥ 2nd	0.000(0.000–0.000)	0.999
1’ Apgar score	1.161(0.757–1.781)	0.493	NEC ≥ 2nd	0.000(0.000–0.000)	0.999

(*Continued*)

Table 2 (Continued).

Characteristic	BPD		Characteristic	BPD	
	OR (95% CI)	*p* value		OR (95% CI)	*p* value
5' Apgar score	1.449(0.515–4.078)	0.482	Ventilation mode	0.260(0.072–0.934)	0.039
SGA	1.158(0.243–5.532)	0.854	Duration of invasive ventilation	0.997(0.990–1.004)	0.428
MSAF	3.778(1.262–11.308)	0.017	Duration of non-invasive ventilation	0.992(0.977–1.007)	0.279
OI	0.965(0.868–1.072)	0.505	Duration of hospitalization	0.950(0.881–1.024)	0.178
Lactate at admission	1.172(0.948–1.449)	0.143			

Abbreviations: BPD, bronchopumonary dysplasia; EOS, early-onset sepsis; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; MAS, meconium aspiration syndrome; NARDS, neonatal acute respiratory distress syndrome; NEC, necrotizing enterocolitis; OI, oxygenation index; PROM, premature rupture of membranes; ROP, retinopathy of prematurity; SGA, small for gestational age.

(Table 4). For the neurobehavioral development, after adjustment for age at admission, gender (male), lactate at admission, maternal age, OI, surfactant treatment, duration of non-invasive ventilation, MSAF and perinatal asphyxia, the results showed that there were no relationship between ventilator mode and neurobehavioral development in neonates with NARDS ($p > 0.05$) (Table 5).

Subgroup Analysis

As shown in Figure 3, to further assess the effect of HFOV-VG mode on BPD, stratification was performed according to gestational age, birth weight, gender, PROM, prenatal glucocorticoid. There were no significant interactions in any of the subgroups except for birth weight subgroup (the incidence of BPD: interaction P = 0.039). The results also showed that the association between HFOV-VG mode and the incidence of BPD was more pronounced in neonates with birth weight < 2500g (OR = 0.097, 95% CI: 0.020–0.462, $p = 0.003$).

Discussion

Our study is the first to compare the incidence of BPD, neurobehavioral development and other complications in infants with NARDS treated with HFOV or HFOV-VG. Our results indicate that the ventilation strategy of HFOV-VG can shorten the duration of invasive ventilation, reduce the incidence of BPD, and have no significant effect on neurobehavioral development in infants with NARDS.

The ventilation strategy plays an important role in the occurrence of BPD and neurodevelopmental impairment. Implementing lung-protective ventilation strategies during mechanical ventilation, specifically targeting the minimization of tidal volume and optimizing lung volume to mitigate volutrauma, is fundamental for reducing the incidence of BPD. Concurrently, maintaining stable $PaCO_2$ levels is paramount to avoid the detrimental effects of both hypercapnia and hypocapnia. Significant fluctuations in $PaCO_2$ can disrupt cerebrovascular autoregulation, potentially leading to cerebral blood flow instability and increasing the risk of brain injury. Therefore, optimizing and individualizing lung-protective ventilation strategies tailored to the unique pathophysiology of neonates remains a crucial and urgent priority in NICU.

HFOV is an important treatment of ARDS. However, the lungs of infants with ARDS contain a mixture of normal alveoli, inflamed tissue, congestion, and atelectasis. Conventional HFOV delivers relatively large tidal volumes, which can easily cause overdistension of airways and alveoli, leading to ventilation related internal environment disorders and lung injury. Researches have found that mechanical ventilation-related lung injury and internal environment disorders were associated with BPD and IVH.[20,21] Therefore, in order to control the tidal volume of HFOV and prevent excessive ventilation in the treatment of ARDS, a novel invasive respiratory support mode – HFOV-VG has been developed. Compared with traditional HFOV, HFOV-VG can maintain a constant tidal volume and minimizes the repeated opening and closing of alveoli, which is the most important aspect of lung-protective ventilation strategies. Furthermore, in preterm infants with severe respiratory failure, the lung recruitment process can be effectively guided by ΔPhf on HFOV-VG.[22] Meanwhile, HFOV-VG promotes airway clearance of secretions and inflammatory mediators through high-frequency oscillations, improves lung compliance, and enhances ventilation/perfusion matching. This contributes to reducing the adverse effects of hypoxia on lung tissue. In

Table 3 Univariate Logistics Regression Analysis of the Association Between Ventilation Mode and Neurobehavioral Development

Characteristic	**Gross Motor**		**Fine Motor**		**Adaptive Behavior**		**Language**		**Personal-Social Behavior**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Gestational age	0.992(0.921–1.069)	0.841	1.009(0.928–1.097)	0.832	0.980(0.911–1.054)	0.585	1.001(0.932–1.074)	0.986	0.997(0.925–1.075)	0.932
Gender	0.000(0.000–0.000)	0.997	0.000(0.000–0.000)	0.997	0.000(0.000–0.000)	0.997	0.000(0.000–0.000)	0.997	4.312(0.508–36.635)	0.181
Birth weight	1.000(0.999–1.002)	0.544	1.001(0.999–1.002)	0.411	1.000(0.999–1.002)	0.819	1.000(0.999–1.001)	0.920	1.000(0.999–1.002)	0.676
Maternal age	0.881(0.740–1.049)	0.154	0.844(0.700–1.018)	0.076	0.854(0.717–1.017)	0.076	0.843(0.714–0.995)	0.043	0.840(0.705–1.001)	0.052
Multiple births	0.557(0.065–4.771)	0.593	0.674(0.076–5.944)	0.722	0.557(0.065–4.771)	0.593	0.474(0.056–3.972)	0.491	0.557(0.065–4.771)	0.503
Vaginal birth	2.350(0.431–12.812)	0.323	2.958(0.513–17.052)	0.225	2.350(0.431–12.812)	0.323	3.678(0.823–16.447)	0.088	2.350(0.431–12.812)	0.323
Age at admission	0.117(0.000–69.169)	0.510	0.095(0.000–121.605)	0.519	0.144(0.000–64.176)	0.533	0.319(0.005–21.709)	0.596	0.057(0.000–71.683)	0.432
Age at NARDS diagnosis	1.044(0.913–1.193)	0.528	1.049(0.909–1.212)	0.512	1.005(0.877–1.152)	0.942	0.993(0.8722–1.130)	0.912	1.078(0.944–1.233)	0.268
PROM	1.084(0.235–4.998)	0.917	0.804(0.158–4.102)	0.793	0.595(0.129–2.743)	0.506	0.802(0.194–3.318	0.761	1.084(0.234–4.998)	0.917
Prenatal glucocorticoid	1.776(0.383–8.230)	0.463	1.160(0.206–6.540)	0.866	1.776(0.383–8.230)	0.463	1.408(0.324–6.124)	0.648	1.776(0.383–8.230)	0.463
Postnatal glucocorticoid	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	3.271(0.351–30.510)	0.298	2.786(0.305–25.457)	0.364	0.000(0.000–0.000)	0.999
1' Apgar score	0.945(0.594–1.502)	0.811	0.899(0.571–1.416)	0.645	0.945(0.594–1.502)	0.811	0.834(0.585–1.188)	0.315	0.945(0.594–1.502)	0.811
5' Apgar score	0.900(0.356–2.275)	0.824	0.842(0.337–2.106)	0.713	0.900(0.356–2.275)	0.824	0.630(0.342–1.160)	0.138	0.900(0.356–2.275)	0.824
SGA	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999
MSAF	1.029(0.118–8.944)	0.979	1.243(0.139–11.130)	0.845	1.029(0.118–8.944)	0.979	2.152(0.408–11.339)	0.366	1.029(0.118–8.944)	0.979
OI	1.111(0.960–1.285)	0.157	1.119(0.957–1.309)	0.159	1.136(0.981–1.315)	0.089	1.127(0.982–1.292)	0.089	1.129(0.976–1.307)	0.103
Lactate at admission	1.278(0.990–1.649)	0.059	1.231(0.926–1.636)	0.152	1.265(0.977–1.638)	0.075	1.279(1.002–1.633)	0.049	1.180(0.882–1.578)	0.265
HsPDA	4.417(0.457–42.687)	0.199	5.333(0.537–53.011)	0.153	4.417(0.457–42.687)	0.199	3.762(0.397–35.631)	0.248	4.417(0.457–42.687)	0.199
Surfactant treatment	5.928(0.698–50.326)	0.103	4.881(0.558–42.684)	0.152	5.928(0.698–50.326)	0.103	2.928(0.574–14.932)	0.196	5.928(0.698–50.326)	0.103
EOS	0.779(0.146–4.141)	0.769	0.982(0.175–5.527)	0.984	1.500(0.324–6.938)	0.604	1.189(0.274–5.159)	0.817	1.500(0.324–6.938)	0.604
Pulmonary hemorrhage	1.800(0.333–9.725)	0.495	0.871(0.098–7.722)	0.901	0.720(0.084–6.202)	0.765	0.613(0.073–5.165)	0.653	0.720(0.084–6.202)	0.765
MAS	1.451(0.165–12.781)	0.737	1.753(0.193–15.898)	0.618	1.451(0.165–12.781)	0.737	3.083(0.574–16.567)	0.189	1.451(0.165–12.781)	0.737
Pneumonia	0.800(0.149–4.284)	0.794	1.640(0.186–14.447)	0.656	1.984(0.232–16.967)	0.532	2.333(0.279–19.535)	0.434	1.984(0.232–16.967)	0.532
Perinatal asphyxia	0.935(0.203–4.311)	0.931	1.423(0.253–7.987)	0.689	1.797(0.339–9.533)	0.491	1.181(0.273–5.107)	0.824	1.797(0.339–9.533)	0.491
Aspiration of blood	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999
Air leak	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999
IVH ≥ 3rd	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999
ROP ≥ 2nd	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999
NEC ≥ 2nd	0.000(0.000–0.000)	0.999	0.000(0.000–0.000)	0.999	1.949(0.218–17.438)	0.551	1.659(0.189–14.541)	0.647	1.949(0.218–17.438)	0.551
Ventilation mode	1.097(0.238–5.060)	0.906	0.721(0.128–4.046)	0.710	0.571(0.108–3.028)	0.510	0.471(0.092–2.402)	0.365	0.571(0.108–3.028)	0.510
Duration of invasive ventilation	1.002(0.995–1.009)	0.622	1.002(0.995–1.010)	0.502	1.003(0.996–1.009)	0.400	1.002(0.996–1.009)	0.485	1.004(0.997–1.010)	0.264
Duration of non-invasive ventilation	1.002(0.988–1.016)	0.779	1.003(0.990–1.017)	0.665	1.003(0.990–1.016)	0.685	1.002(0.989–1.015)	0.819	1.006(0.996–1.016)	0.263
Duration of hospitalization	1.017(0.945–1.094)	0.652	1.020(0.945–1.101)	0.609	1.027(0.960–1.100)	0.436	1.016(0.948–1.088)	0.660	1.029(0.961–1.101)	0.412

Abbreviations: BPD, bronchopumonary dysplasia; EOS, early-onset sepsis; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; MAS, meconium aspiration syndrome; MSAF, meconium-stained amniotic fluid; NARDS, neonatal acute respiratory distress syndrome; NEC, necrotizing enterocolitis; OI, oxygenation index; PROM, premature rupture of membranes; ROP, retinopathy of prematurity; SGA, small for gestational age.

Table 4 Multivariable Logistics Regression Analysis of the Association Between Ventilation Mode and BPD

	Model 1		**Model 2**		**Model 3**	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
HFOV	Reference		Reference		Reference	
HFOV-VG	0.229(0.062–0.843)	0.027	0.231(0.063–0.852)	0.028	0.143(0.035–0.578)	0.006

Notes: Model 1 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male); Model 2 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male), surfactant treatment; Model 3 adjusted for gestational age, birth weight, prenatal glucocorticoid, gender (male), surfactant treatment, meconium-stained amniotic fluid and EOS.

Abbreviations: HFOV, high-frequency oscillatory ventilation; HFOV-VG, High-frequency oscillatory ventilation with volume-guaranteen; OI, oxygenation index; OR, odds ratios for the development of BPD; 95% CI, 95% confidence intervals.

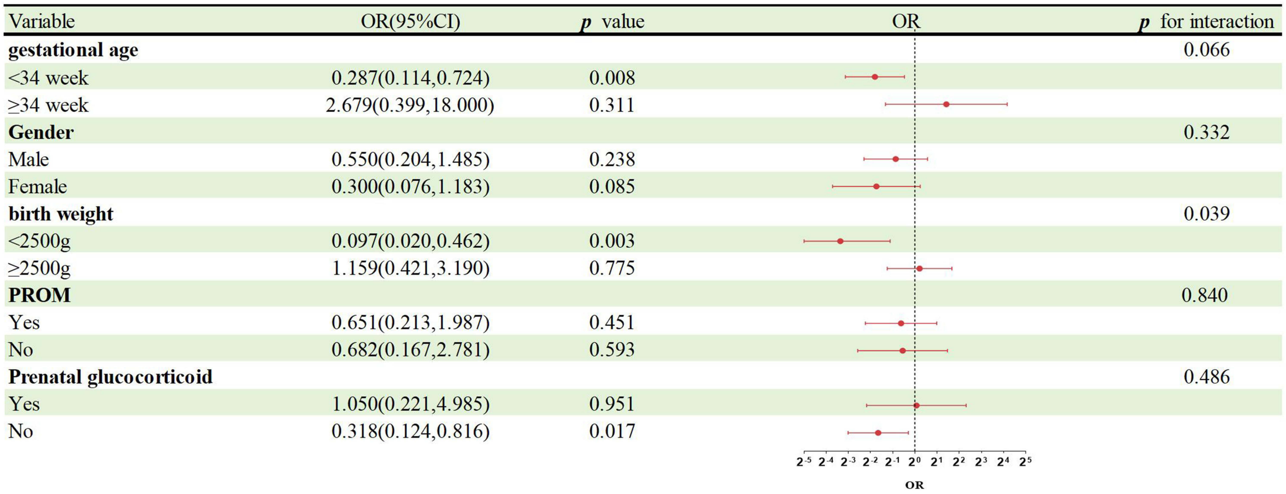
Table 5 Multivariable Logistics Regression Analysis of the Association Between Ventilation Mode and Neurobehavioral Development

	Model 1		**Model 2**		**Model 3**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Gross motor						
HFOV	Reference		Reference		Reference	
HFOV-VG	1.013(0.207–4.966)	0.987	1.170(0.225–6.079)	0.852	1.150(0.021–64.137)	0.946
Fine motor						
HFOV	Reference		Reference		Reference	
HFOV-VG	0.608(0.102–3.622)	0.585	0.676(0.110–3.149)	0.673	0.615(0.012–31.819)	0.809
Adaptive behavior						
HFOV	Reference		Reference		Reference	
HFOV-VG	0.471(0.082–2.695)	0.398	0.537(0.091–3.151)	0.491	0.568(0.011–29.577)	0.779
Language						
HFOV	Reference		Reference		Reference	
HFOV-VG	0.376(0.067–2.091)	0.264	0.399(0.071–2.231)	0.295	0.055(0.002–1.552)	0.089
Personal-social behavior						
HFOV	Reference		Reference		Reference	
HFOV-VG	0.461(0.082–2.606)	0.381	0.521(0.089–3.035)	0.468	0.423(0.011–17.004)	0.648

Notes: Model 1 adjusted for age at admission, gender (male), lactate at admission, maternal age and OI. Model 2 adjusted for age at admission, gender (male), lactate at admission, maternal age, OI, surfactant treatment and duration of non-invasive ventilation. Model 3 adjusted for age at admission, gender (male), lactate at admission, maternal age, OI, surfactant treatment, duration of non-invasive ventilation, meconium-stained amniotic fluid and perinatal asphyxia.

Abbreviations: HFOV, high-frequency oscillatory ventilation; HFOV-VG, High-frequency oscillatory ventilation with volume-guaranteen; OI, oxygenation index; OR, odds ratios; 95% CI, 95% confidence intervals.

addition, as lung compliance changes during disease progression, HFOV-VG automatically adjusts the MAP to maintain a constant alveolar volume available for gas exchange, thereby stabilizing $PaCO_2$. Lin et al[23] found that HFOV-VG reduced VThf levels and decreased the incidence of hypercapnia and hypocapnia in premature infants with acute hypoxic respiratory failure after patent ductus arteriosus ligation.



Variable	OR(95%CI)	*p* value	*p* for interaction
gestational age			0.066
<34 week	0.287(0.114,0.724)	0.008	
≥34 week	2.679(0.399,18.000)	0.311	
Gender			0.332
Male	0.550(0.204,1.485)	0.238	
Female	0.300(0.076,1.183)	0.085	
birth weight			0.039
<2500g	0.097(0.020,0.462)	0.003	
≥2500g	1.159(0.421,3.190)	0.775	
PROM			0.840
Yes	0.651(0.213,1.987)	0.451	
No	0.682(0.167,2.781)	0.593	
Prenatal glucocorticoid			0.486
Yes	1.050(0.221,4.985)	0.951	
No	0.318(0.124,0.816)	0.017	

Figure 3 The forest plots show the associations between ventilation mode with BPD according to different subgroups. Subgroup analysis included gestational age (< 34 week vs ≥ 34 week), gender (male vs female), birth weight (< 2500g vs ≥ 2500g), PROM (Yes vs No) and prenatal glucocorticoid (Yes vs No).
Abbreviation: PROM, premature rupture of membranes.

The HFOV-VG strategy represents a key technology for mitigating ventilator-associated lung injury and ensuring stable $PaCO_2$. Currently, this strategy is being increasingly adopted in neonatal care, offering significant benefits through precise tidal volume control that prevents both hyperinflation and hypoventilation. A study on extremely premature infants associated with severe respiratory distress syndrome found that HFOV-VG can cause better pulmonary outcomes at 36 weeks and additional improved respiratory prognosis at two years of age.[23] Zheng et al[24] found that compared with HFOV alone, HFOV-VG can alleviate pulmonary inflammation and shorten postoperative mechanical ventilation time in infants with ARDS after congenital heart disease surgery. So, can the HFOV-VG strategy also provide similar benefits in the treatment of ARDS? There is currently no relevant research available. Our research indicates that compared to HFOV, HFOV-VG can shorten the duration of invasive ventilation and reduce the incidence of BPD in infants with NARDS. Multivariate logistic regression analysis found that after adjustment for gestational age, birth weight, prenatal glucocorticoid, gender (male), surfactant treatment, meconium-stained amniotic fluid and EOS, HFOV-VG mode was still an independent protective factor for BPD. The potential mechanisms underlying these benefits may include the following: (1) Lung Injury Mitigation: The heterogeneous nature of pulmonary lesions in neonates with NARDS renders conventional ventilation modes prone to damaging relatively normal alveoli. Crucially, elevated tidal volumes represent an established independent risk factor for VILI in ARDS.[25] Conventional HFOV, often delivering larger tidal volumes, can lead to overdistension of airways and alveoli, thereby contributing to VILI. (2) Reduced Ventilation Duration: Prolonged invasive mechanical ventilation exacerbates pulmonary inflammation and oxidative stress injury, potentially triggering airway remodeling and impairing lung development, which are key pathways in the pathogenesis of BPD.[26] Yang et al[27] reported that invasive mechanical ventilation exceeding 7 days significantly increased the risk of BPD and mortality. Crucially, our study found that HFOV-VG significantly shortened the duration of mechanical ventilation compared to HFOV. (3) Anti-Inflammatory Effects: Inflammation is a central driver of BPD pathogenesis. Preclinical evidence suggests HFOV-VG attenuates pulmonary exudation and confers lung protection in premature infants with respiratory distress syndrome,[4] indicating its potential to reduce BPD incidence by mitigating systemic inflammation. This anti-inflammatory benefit is corroborated by clinical studies. Lista et al[28] observed lower expression of early inflammatory markers in preterm infants managed with HFOV-VG compared to conventional HFOV. Similarly, Zheng et al[29] demonstrated that HFOV-VG reduced the systemic inflammatory response more effectively than HFOV alone in infants with ARDS following congenital heart disease surgery. Therefore, we propose that HFOV-VG, as an advanced ventilation strategy, may offer superior lung tissue protection compared to conventional HFOV in the management of ARDS.

Researches have found that hypercapnia induces cerebral vasodilation and increases cerebral blood flow (CBF), which is associated with adverse neurological and respiratory outcomes, as well as retinopathy of prematurity in preterm

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infants.[30,31] Conversely, hypocapnia causes cerebral vasoconstriction, reducing CBF and potentially leading to neurological complications such as IVH, periventricular white matter injury, and cerebral palsy. HFOV-VG stabilizes $PaCO_2$, thereby reducing the incidence of both hypercapnia and hypocapnia.[23] This suggests that HFOV-VG may mitigate adverse neurological outcomes by minimizing $PaCO_2$ fluctuations and their impact on CBF. However, our study did not demonstrate a significant advantage of the HFOV-VG strategy in reducing the risk of neurodevelopmental impairment, which may be attributable to the gestational age range included in our cohort. To minimize heterogeneity and confounding factors, this study specifically enrolled preterm infants with a gestational age ≥ 32 weeks-a population inherently at lower risk for severe neurodevelopmental impairment. Additionally, neurodevelopmental assessments were conducted only at 6 months corrected age. Extending the follow-up period is crucial to further evaluate the potential long-term impact of the HFOV-VG strategy on neurological development in infants with NARDS.

This study has several limitations. Firstly, as a single-center retrospective analysis, our findings may be influenced by unmeasured confounders and institutional-specific practices, limiting generalizability. Although we implemented rigorous covariate adjustment and standardized diagnostic criteria, residual confounding cannot be fully excluded. Secondly, the sample size and low event rate of BPD reduced statistical power, particularly for subgroup analyses and neurodevelopmental outcomes where observed effect sizes were modest. Thirdly, neurodevelopmental assessment at only 6 months corrected age is insufficient to evaluate long-term outcomes. The absence of data at 12–24 months precludes conclusions about cerebral palsy or cognitive delay, which are more reliably assessed at later ages. We are currently planning a prospective study to assess neurodevelopmental outcomes at 12–24 months corrected age. Fourthly, although ventilator parameters comply with guideline requirements, differences in management practices may still arise among clinicians. Standardization of these operational details would strengthen future investigations. Finally, by excluding infants < 32 weeks to minimize diagnostic confusion between NARDS and NRDS, our results may not generalize to extremely preterm populations at highest BPD risk. Prospective multicenter trials with protocolized ventilation management, larger samples and extended neurodevelopmental follow-up are warranted to validate these findings.

Conclusions

Compared with HFOV alone, HFOV-VG strategy shortened mechanical ventilation duration and demonstrated a potential benefit in reducing the risk of BPD in premature infants with moderate-to-severe neonatal ARDS. Although no adverse effects on neurobehavioral development were observed at 6 months corrected age, this assessment timeframe is insufficient to evaluate long-term neurodevelopmental outcomes. Future multicenter randomized controlled trials with extended neurodevelopmental follow-up, larger sample sizes, and protocolized ventilation management are warranted to validate these findings and definitively assess the strategy's neurodevelopmental safety profile.

Ethics Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University, Chongqing, China, and all research procedures were conducted according to the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the need for informed consent was waived by First Hospital Affiliated of Army Medical University. All data were stored securely, and confidentiality was maintained throughout the study.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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