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Application of High-Frequency Oscillation Ventilation Combined With Volume Guarantee in Preterm Infants With Acute Hypoxic Respiratory Failure After Patent Ductus Arteriosus Ligation

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of high-frequency oscillation ventilation combined with volume guarantee (HFOV-VG) in preterm infants with acute hypoxemic respiratory failure (AHRF) after patent ductus arteriosus ligation.

Methods: We retrospectively analyzed the clinical data of 41 preterm infants, who were ventilated for AHRF after patent ductus arteriosus ligation between January 2020 and January 2022. HFOV alone was used in 20 of the 41 infants, whereas HFOV-VG was used in the other 21 infants.

Results: There was no statistically significant difference in the demographic information and baseline characteristics of preterm infants included in the study. The average frequency tidal volume (VThf) of the HFOV-VG group was lower than that of the HFOV group (2.6 ± 0.6 mL versus 1.9 ± 0.3 mL, $P < .001$). In addition, the incidence of hypocapnia and hypercapnia in infants supported with HFOV-VG was significantly lower (15 versus 8, $P < .001$; 12 versus 5, $P < .001$). Furthermore, the duration of invasive ventilation in the HFOV-VG group also was lower than in the HFOV group (3.7 ± 1.2 days versus 2.1 ± 1.0 days, $P < .01$).

Conclusion: Compared with HFOV alone, HFOV-VG decreases VThf levels and reduces the incidence of hypercapnia and hypocapnia in preterm infants with acute hypoxic respiratory failure after patent ductus arteriosus ligation.

INTRODUCTION

Patent ductus arteriosus (PDA) is a relatively common problem in preterm infants, and its incidence is inversely correlated with birth weight (BW) and gestational age (GA). PDA has been reported in approximately 46% of preterm infants < 32 weeks' gestation and more than 70% of preterm infants < 28 weeks' gestation [Clyman 2012; Sellmer 2013]. Continuous left-to-right ductal shunt diverts blood from the systemic to the pulmonary circulation, resulting in pulmonary congestion and systemic hypoperfusion, which reduces lung compliance and leads to tissue ischemia [Clyman 2017]. Therefore, in preterm infants with hemodynamically significant PDA, surgical ligation remains an essential treatment option in the event of failure of medical therapy or contraindications to medical therapy. Since many preterm infants who need PDA surgical ligation rely on mechanical ventilation, there are unfavorable factors, such as immature lung development, and a large volume of left-to-right shunts caused by PDA leads to pulmonary congestion. Acute hypoxic respiratory failure (AHRF) or acute respiratory distress syndrome (ARDS) and other serious pulmonary complications often occur after PDA ligation.

High-frequency oscillatory ventilation (HFOV) is considered a rescue therapy for infants with AHRF and/or ARDS [Randolph 2009]. Potential advantages over conventional mechanical ventilation (CMV) include the application of lower tidal volumes and the safe use of higher mean airway pressure (MAP) than commonly used in CMV to achieve lung recruitment and improved oxygenation [Rehan 2011]. Carbon dioxide (CO_2) removal during HFOV is determined by the diffusion coefficient of CO_2 (DCO_2), which is calculated as frequency multiplied by the squared volume of high-frequency tides (VThf). However, the amount of VThf may also be related to the size of the tracheal tube and lung compliance. These factors cause large changes in tidal volume and CO_2 elimination, leading to risks such as hypercapnia or hypocapnia. To address these issues, a new ventilation modality, high-frequency oscillatory ventilation combined with volume guarantee (HFOV-VG), was introduced. In the process of applying HFOV-VG, we set the target VThf, and the ventilator automatically adjusts the amplitude to reach the preset VThf [Belteki 2019]. Recently, the application of HFOV-VG in animal models and neonates has been reported [Iscan 2015; Chen 2019; Sánchez 2013; Enomoto 2017].

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However, no studies have analyzed the efficacy of HFOV-VG for AHRF in preterm infants following ductal ligation surgery. The purpose of this study was to evaluate the efficacy and safety of HFOV-VG versus HFOV alone in AHRF after ductus arteriosus ligation in preterm infants.

MATERIALS AND METHODS

Patients and data collection

We performed a retrospective analysis of data on intubated preterm infants who underwent PDA ligation in our cardiac intensive care unit (CICU) and developed AHRF between January 2020 and January 2022. This study was approved by the Ethics Committee of our institution (No. 2020KY039) and complies with the Declaration of Helsinki. The information in the research content was informed to parents in detail, their consent was obtained, and an informed consent form was signed.

The inclusion criteria were postoperative infants, who underwent PDA ligation and had AHRF postoperatively and failed CMV. All patients were hemodynamically stable after the operation, and the anatomical correction effect was satisfactory. Exclusion criteria included hemodynamically significant residual disease, pulmonary vein obstruction, tracheal tube leakage greater than 30%, air leak syndrome, and ARDS requiring ECMO. AHRF was defined by acute onset, symptoms of hypoxemia, and radiographic changes occurring within 7 days of a known clinical insult. The chest imaging findings of a new infiltrate were consistent with the acute pulmonary parenchymal disease, combined with PaO_2/FiO_2 < 300 mmHg, which cannot be explained by the underlying cardiac disease. The diagnosis of ARDS was established, according to the 2017 Montreux definition of neonatal ARDS and the 2015 Pediatric Acute Lung Injury Consensus Conference Group definition of ARDS [De Luca 2017; Pediatric Acute Lung Injury Consensus Conference Group 2015]. The diagnosis of ventilator-associated pneumonia is based on criteria established by the Centers for Disease Control and Prevention, supplemented by chest radiograph, positive sputum culture, transtracheal effusion, bronchial washes, and clinical findings [Horan 2008].

Ventilation strategies

For infants who failed conventional mechanical ventilation (CMV), we used HFOV as the rescue ventilation mode. Conventional mechanical ventilation failure was defined as follows: refractory respiratory failure with high peak positive pressure requirement (over 28 cmH_2O) or high VT (> 8 mL/kg) required on conventional ventilation, diffuse atelectasis requiring recruitment, or high fraction of inspired oxygen (FiO_2) requirements despite appropriate PEEP, and refractory respiratory acidosis ($PaCO_2$ > 60 mmHg and/or pH < 7.20). HFOV was provided by an SLE 6,000 (SLE UK, Croyden, United Kingdom) ventilator that used a venturi system to generate oscillating pressure amplitudes and the resulting tidal volume during HFOV. The initial parameters of HFOV are: frequency 8 ~ 10 Hz, inspiratory: expiratory ratio 1:1, amplitude 30 ~ 40 mbar, fraction of inspired oxygen (FiO_2) 0.4 ~ 60%, MAP 2 cmH2O higher than conventional ventilation. After 1 hour of mechanical ventilation, chest radiographs were performed with ideal lung inflation, and the right diaphragm generally was maintained at the level of the ninth rib. Transcutaneous carbon dioxide ($PcCO_2$) monitoring should be used in infants receiving HFOV. The target partial pressure of carbon dioxide (PCO_2) ranged from 35 to 45 mmHg. If PCO_2 fluctuated greatly under HFOV, such as hypercapnia/hypocapnia, we transferred to HFOV-VG for respiratory support. When arterial blood gas (ABG) confirmed that an infant's $PaCO_2$ was within the target range, the current VThf was used as the target value. The microprocessor inside the ventilator compares the VThf of the previous breath, uses the exhaled VThf, and automatically adjusts the amplitude to achieve the set VThf. Based on our clinical experience, the initial VThf was set to 2 mL/kg in HFOV-VG mode, with a target range of 1.5–2.5 mL/kg. The amplitude limit is set to 10%-20% higher than the average amplitude. Subsequently, based on ABG and PCO_2 data, the tidal volume should not exceed 0.5 mL/kg per weaning. The cannula was removed when the infant was hemodynamically stable, MAP < 10 cm H_2O, FiO_2 < 40%, and weaned sedation. The patient was transferred to conventional ventilation before extubation. During the study, both groups of patients were managed by the same group of pediatricians, and ventilation strategies and procedures were always consistent.

Data collection

We conducted a detailed retrospective review of all medical records through the hospital's medical record system. Additionally, in our CICU, we routinely have a ventilator parameter sheet to record the ventilator's real-time parameters. Baseline data points included demographics, left atrium-to-aorta ratio, PDA size/body weight, pre-operation pulmonary hypertension, the cardiothoracic ratio on the radiograph, prior ibuprofen treatment history of lung disease, pre-operation oxygen index, pre-operation NRDS, pre-operation IVH (intraventricular hemorrhage), infants with ventilator-dependent, and duration of HFOV-VG were recorded. Ventilation settings and measurements: amplitude, mean airway pressure (MAP), tidal volume (VThf); vital signs such as heart rate, mean arterial blood pressure, CVP (central venous pressure), and available arterial blood gas data (pH, PaO_2, $PaCO_2$, PaO_2/FiO_2 ratio, lactate) were recorded in the electronic medical record system. Arterial blood gas (ABG) was evaluated 30 minutes after HFOV-VG was started using a blood gas analyzer (ABLTM 900 radiometer, Copenhagen, Denmark) and repeated every 4-6 hours or more often, as needed. Hypoxemia was defined as PaO_2 < 50 mmHg and/or PaO_2/FiO_2 < 200 mmHg. Hypocarbia was defined as $PaCO_2$ < 35 mmHg, and hypercarbia was defined as $PaCO_2$ > 60 mmHg. Infants were monitored using pulse oximetry and blood pressure measurements. Data from the ventilator were exported to the mobile storage device for further analysis.

Statistical analysis

The sample size was not predetermined; we included all eligible infants in the study. Data were analyzed using

Table 1. Demographic and baseline characteristics*

Characteristics	HFOV (N = 20)	HFOV-VG (N = 21)	*P*-value
Sex (male/female)	9/11	13/8	.354
GA at birth (weeks; mean ± SD)	29.4 ± 2.8	29.1 ± 3.1	.749
BW at birth (gram; mean ± SD)	1320 ± 250	1290 ± 295	.736
Age at surgery (days; mean ± SD)	27.6 ± 8.2	25.2 ± 9.5	.374
BW at surgery (kg; mean ± SD)	1652 ± 303	1590 ± 351	.549
LA/AO ratio (mean ± SD)	1.75 ± 0.07	1.72 ± 0.07	.072
PDA size/BW (mm/kg)	2.5 ± 0.4	2.8 ± 0.3	.100
Pre-op pulmonary hypertension, n (%)	15 (75)	17 (81)	.719
Prior ibuprofen treatment, n (%)	18 (90)	17 (81)	.663
OI before HFOV (mean ± SD)	8.5 ± 3.7	9.0 ± 3.4	.621
PO_2/ FiO_2 before HFOV	195.5 ± 38.3	189.2 ± 40.8	.611
Pre-op IVH, n (%)	4 (20)	6 (29)	.719

HFOV, high-frequency oscillation ventilation; VG, volume guarantee; GA, gestational age; BW, body weight; LA/AO, left atrium-to-aorta; PDA, patent ductus arteriosus; NRDS, neonatal respiratory distress syndrome; IVH, intraventricular hemorrhage. *Data reported as number and percentage or mean ± standard deviation.

SPSS software version 25.0 for Windows (IBM SPSS Inc., Chicago, IL, USA). Independent continuous variables are presented as the mean ± standard deviation (SD) and were analyzed by t-tests. Counts and percentages describe the enumeration data. Means were compared using Student's t-test, and Fisher's exact test was used for categorical data. The Mann–Whitney U test was applied for non-normally distributed data. A two-sided *P*-value of <.05 was regarded as statistically significant.

RESULTS

Patient characteristics

During the study period, we found that 45 infants met the inclusion criteria, but four of them were excluded due to lack of complete data or the parents decided to drop out of the study. So, we finally included a total of 41 infants ventilated for AHRF after congenital heart surgery. Among them, HFOV alone was used in 20 of the 41 infants, whereas HFOV-VG was used in the other 21 infants.

The characteristics of the patients in both groups are presented in Table 1. The mean weights at the surgery in the HFOV and HFOV-VG groups were 1652 ± 303 g and 1590 ± 351 g, respectively, and the ages at HFOV therapy in the HFOV alone and HFOV-VG groups were 27.1 ± 8.2 days and 25.2 ± 9.5 days, respectively ($P > .05$). No significant differences were observed between the two groups, in terms of the other demographic and clinical characteristics of the included infants.

Outcomes

The effects of different ventilation modes on ABGs and respiratory mechanics indexes in the two groups are shown in Table 2. The amplitude and PCO_2 in the HFOV-VG group were lower than those in the HFOV group (40.8 ± 4.2 versus 37.8 ± 2.6, $P = .008$; 48.4 ± 6.8 versus 41.2 ± 5.5, $P = .001$). The average VThf of the HFOV-VG group was lower than that of the HFOV group (2.6 ± 0.6 versus 1.9 ± 0.3, $P < .001$). Fifteen episodes of hypercapnia were recorded in the HFOV alone group, and eight episodes were recorded in the HFOV-VG group ($P < .001$). Meanwhile, there were 12 episodes of hypocarbia in the HFOV alone group and five episodes in the HFOV-VG group ($P < .001$). There were no significant differences between the ventilation modes in terms of MAP, DCO_2, FiO_2, PH, PO_2, PO_2/FiO_2 ratio, lactates, and episodes of hypoxemia during the study period ($P > .05$).

The complications and short-term outcomes of studying infants are presented in Table 3. The duration of invasive ventilation was shorter in the HFOV-VG group (3.7 ± 1.2 days versus 2.1 ± 1.0 days, $P < .01$). We did not find significant differences in the incidence of post-operation intraventricular hemorrhage, periventricular leukomalacia, post-operation necrotizing enterocolitis, ventilator-associated pneumonia, bronchopulmonary dysplasia, retinopathy of prematurity, and death ($P > .05$). There was no significant difference in surgical complications between the two groups ($P = .572$). All infants were successfully extubated after PDA ligation and survived. However, one infant died of sepsis 36 days after surgery, and the cause of death was not related to PDA ligation.

DISCUSSION

Based on our study, HFOV-VG can reduce VThf levels after PDA ligation in preterm infants and decreases the incidence of hypercapnia and hypocapnia. When medical therapy is contraindicated or fails to induce sufficient duct constriction

Table 2. Ventilation variables and blood gas analysis results during the study period†

Variable	HFOV (N = 20)	HFOV-VG (N = 21)	*P*-value
MAP (cmH_2O)	15.2 ± 2.2	14.3 ± 2.4	.267
DCO_2 ($mL^2.s$)	865 ± 202	785 ± 164	.173
Amplitude (mbar)	40.8 ± 4.2	37.8 ± 2.6	.008
FiO_2 (%)	69.5 ± 10.5	65.4 ± 8.1	.168
pH	7.42 ± 0.06	7.40 ± 0.04	.138
PO_2 (mmHg)	75.8 ± 7.6	77.5 ± 8.1	.492
PCO_2 (mmHg)	48.4 ± 6.8	41.2 ± 5.5	.001
PaO_2/FiO_2 ratio	255.7 ± 40.3	267.5 ± 38.3	.346
Lactates, (mmol/L)	1.1 ± 0.5	1.2 ± 0.4	.633
VThf (mL/kg)	2.5 ± 0.6	1.9 ± 0.3	<.001
Episode of hypoxemia#	13 ± 3	11 ± 2	.073
Episode of hypocapnia#	12 ± 4	5 ± 2	<.001
Episode of hypercapnia#	15 ± 5	8 ± 2	<.001

HFOV, high-frequency oscillation ventilation; VG, volume guarantee; MAP, mean airway pressure; VThf, high-frequency tidal volume; DCO_2, diffusion coefficient of CO_2; FiO_2, fraction of inspired oxygen; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide. †Data reported as mean ± standard deviation; *, the target range of VThf was 1.5–2.5mL/kg; #, refers to the total number of such events occurring in patients during HFOV.

to reduce shunt flow, surgical ligation is an important part of the management of PDA because it provides immediate and unequivocal interruption of the ductal shunt. However, the choice of surgical treatment for preterm infants remains one of the most enduring controversies in neonatal medicine [Elsaka 2021]. Ligation of PDA in preterm infants is usually a simple procedure, but because patients often are small and immature and may have multiple comorbidities, PDA closure can bring about significant physiological changes. Once a decision has been made to perform surgical ligation, it is important to optimize the patient's condition to minimize the risk of surgical complications and cardiorespiratory instability.

For premature infants requiring surgical ligation of PDA, pulmonary underdevelopment, subsequent post-surfactant ventilation-perfusion mismatch, impaired alveolar-capillary membrane oxygen diffusion, and exhaustion of intrapulmonary shunts, excessive circulation, and edema, together with surgical strike may exacerbate respiratory failure or even severe ARDS [Weisz 2018]. Studies have shown that the application of HFOV results in more uniform lung inflation, improved oxygenation, and reduced severity of lung injury caused by intermittent positive pressure ventilation [Chen 2019]. HFOV ventilation modulates VThf by modulating amplitude. However, since the compliance and resistance of the lung tissue are not fixed, the VThf is unstable, which may lead to excessive expansion or collapse of the alveoli at the airway terminal and alveolar level. HFOV-VG mode is a new invasive respiratory support mode, which recently has received increased clinical attention. Compared with HFOV alone, HFOV-VG reduces the fluctuation of VThf and the number of PCO_2 values outside the target range, thus reducing the incidence of hypocapnia and hypercapnia, which may have broad prospects in reducing lung injury [Sánchez-Luna 2018].

Due to the immature lung development of premature infants, ventilator-associated lung injury is more likely to occur, which will exacerbate the developmental disorders of the lungs after birth, leading to serious sequelae such as bronchopulmonary dysplasia [Attar 2020]. Among them, volume injury is one of the important mechanisms of VILI. Our study found that the VThf under HFOV-VG was lower than that of HFOV, and the duration of invasive ventilation was shorter, which was beneficial for reducing ventilator-related lung injury. In HFOV-VG mode, the amplitude automatically is adjusted by the ventilator to ensure the target VThf. By adjusting the proximal airway pressure, the VThf sent by the machine into the airway is kept constant, and the VThf is manually controlled to keep it at an appropriate level. In general, VThf should be close to or even lower than the alveolar anatomical dead volume to reduce traction on alveolar cells and stromal tissue. In addition, VG ventilation can avoid both extremes of VT and achieve a sustained reduction in peak pressure, thereby avoiding volume and pressure injury, and reducing the occurrence of ventilator-related lung injury [Sánchez-Luna 2018; Enomoto 2017]. This may be beneficial to reducing the occurrence of BPD and improving the long-term prognosis of the respiratory system, but it still needs to be confirmed by further studies.

Our study found that HFOV-VG could reduce the incidence of PCO_2 exceeding the target range and thus the incidence of hyper/hypocapnia. PCO_2 is determined by DCO_2 during HFOV ventilation. Since DCO_2 (mL^2/s) is composed

Table 3. Complications and short-term outcomes of the study infants*

Variable	HFOV (N = 20)	HFOV-VG (N = 21)	*P*-value
Post-op IVH, n (%)	3 (15)	4 (19)	1.000
PVL, n (%)	1 (5)	0	/
Post-op NEC, n (%)	2 (10)	1 (5)	.606
VAP, n (%)	2 (10)	2 (10)	1.000
ROP, n (%)	3 (15)	4 (19)	1.000
BPD, n (%)	6 (30)	8 (38)	.744
Pneumothorax, n (%)	2 (8.7)	1 (4.8)	.606
Complications of surgery			
Pneumothorax, n	1	0	
Phrenic nerve palsy, n	1	1	.572
Vocal cord paralysis, n	0	1	
Hemothorax, n	1	1	
Duration of invasive ventilation (days; mean ± SD)	3.7 ± 1.2	2.1 ± 1.0	<.01
Death, n (%)	1 (4.3)	0	/

IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; VAP, ventilator associated pneumonia; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. *Data reported as number and percentage, mean ± standard deviation.

of "DCO_2=f x $VThf^2$", a small change in VThf has a significantly greater effect on DCO_2 than a change in frequency [Singh 2012]. Thus, the setting of the target VThf directly determines the magnitude of DCO_2, which in turn affects the level of PCO_2. A study of 13 neonates ventilated with HFOV-VG found that the mean VThf to maintain normocapnia was 1.67 mL/kg [Zimová-Herknerová 2006]. The initial value of VThf commonly used in clinical practice is generally 1.5-2.0 mL/kg, while the target VThf range used in our study is 2-2.5 mL/kg because infants with congenital heart disease often have postoperative complications [Iscan 2015; Enomoto 2017; Tuzun 2020]. These include pulmonary edema and atelectasis, so they require higher volume support to maintain normocapnia. At present, whether the VThf value changes with age, weight or cardiorespiratory condition needs further study. To ensure the target VThf, the amplitude under HFOV-VG ventilation is generally set at 15%-20% of the average amplitude above the target VThf [Iscan 2015; Enomoto 2017; Tuzun 2020].

This is the first study to use HFOV-VG in preterm infants with AHRF after ductal ligation surgery. However, this study has several limitations. First, this is a retrospective study. The statistical validity is not as good as that of prospective studies, which is an inevitable flaw of this study. Second, this is a single-center study, which may hinder the application of existing research findings to other institutions. In addition, the sample size was small, observation period was short, and follow up was lacking. These limitations may affect the accuracy of the results. Although this was a retrospective study with small sample size, the findings suggest that HFOV-VG is a promising ventilation modality. It provides a certain reference value for further in-depth perspective research in the future and helps to promote the application of HFOV+VG in the perioperative management of PDA ligation.

CONCLUSION

In conclusion, compared with HFOV alone, HFOV-VG decreases VThf levels and reduces the incidence of hypercapnia and hypocapnia in preterm infants with AHRF after PDA ligation. Therefore, we propose the use of this lung-protective strategy to minimize ventilator-associated lung injury in infants who have failed CMV after PDA ligation.

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