

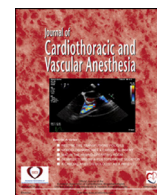


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## Original Article

# Effect of High-Frequency Oscillatory Ventilation, Combined With Prone Positioning, in Infants With Acute Respiratory Distress Syndrome After Congenital Heart Surgery: A Prospective Randomized Controlled Trial

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**Objectives:** This study aimed to evaluate the effect of high-frequency oscillatory ventilation, (HFOV) combined with prone positioning, on oxygenation and pulmonary ventilation in infants with acute respiratory distress syndrome (ARDS) after congenital heart surgery.

**Design:** A randomized controlled trial.

**Setting:** A single-center study at a tertiary teaching hospital.

**Participants:** Patients with postoperative ARDS after congenital heart disease were divided randomly into the following 2 groups: HFOV combined with prone position (HFOV-PP), and HFOV combined with supine position (HFOV-SP).

**Interventions:** The primary outcomes were the PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio and the oxygenation index after the intervention, and the secondary outcomes were respiratory variables, hemodynamics, complications, and other short-term outcomes.

**Results:** Sixty-five eligible infants with ARDS were randomized to either the HFOV-PP (n = 32) or HFOV-SP (n = 33) group. No significant difference in baseline data was found between the 2 groups (p > 0.05). Oxygenation was improved in both groups after HFOV intervention. Compared with the HFOV-SP group, the HFOV-PP group had significantly increased PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> and oxygenation index and a shorter duration of invasive ventilation and length of cardiac intensive care unit stay. No serious complications occurred in the 2 groups.

**Conclusion:** HFOV-PP significantly improved oxygenation in infants with ARDS after cardiac surgery and had no serious complications.

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**Key Words:** High-frequency oscillatory ventilation; Prone position; ARDS; Congenital heart surgery

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is the leading cause of respiratory failure after surgery for congenital heart disease (CHD). Its incidence in patients undergoing cardiac surgery ranges from 0.4% to 20%, and its mortality rate is as high as 80%.<sup>1-4</sup> The cornerstone of ARDS management is lung-protective mechanical ventilation with

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low tidal volumes. High-frequency oscillatory ventilation (HFOV) combines high respiratory frequency and less tidal volume than the anatomic deadspace volume, and maintains a constant distending mean airway pressure (MAP) where oscillations occur. This strategy maintains a high MAP to evenly distribute ventilation and reduce the risk of lung injury and hyperinflation caused by the ventilator.<sup>5</sup> Ventilation in the prone position has been used widely in critically ill infants as a rescue strategy for severe hypoxemia in ARDS. The prone position reduces pleural pressure gradients, restores aeration to dorsal lung segments, and improves the oxygenation of most patients with ARDS (70%-80%) by increasing the average ratio of PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub>.<sup>6-11</sup> For patients with severe ARDS, the early prone position can significantly reduce 28-day and 90-day mortality.<sup>7</sup> Given that these 2 approaches can promote lung recruitment, their combination may have a synergistic effect on gas exchange. This study hypothesized that HFOV, combined with prone position (HFOV-PP), could improve oxygenation compared with HFOV combined with supine position (HFOV-SP) in infants with ARDS after congenital heart surgery, and is safe in post-thoracotomy patients. Therefore, the primary objective of this prospective randomized controlled study was to evaluate the efficacy and safety of HFOV-PP in infants with ARDS after congenital heart surgery.

## Methods

### Study Design

This single-center, prospective randomized controlled study was conducted in the cardiac intensive care unit (CICU) of \*\*\* Hospital from January 2020 to July 2021. The protocol was approved by the ethics committee of \*\*\* Hospital and adhered to the tenets of the Declaration of Helsinki (as revised in 2013). Written informed consent was preoperatively obtained from all patients or their guardians.

### Study Patients

Inclusion criteria for infants were as follows: (1) patients with well-recovered postoperative cardiac function and who were hemodynamically stable, and (2) infants with ARDS who initially were subjected to unsuccessful conventional mechanical ventilation (CMV) and then treated with HFOV. Exclusion criteria were as follows: (1) hemodynamically significant residual lesions or pacemaker dependency; (2) delayed chest closure after surgery for CHD; (3) facial or spinal injury; (4) pulmonary venous obstruction, air leak syndromes, hemothorax, or large pleural effusion; (5) ARDS requiring extracorporeal membrane oxygenation treatment; and (6) parents' decision not to participate.

### Allocation

After the failure of lung-protective CMV (ventilation failure is defined as refractory respiratory failure, high peak positive pressure demand [ $\geq 28$  cmH<sub>2</sub>O], or high tidal volume (VT)

demand during routine ventilation [VT > 10 mL/kg]), diffuse atelectasis requires lung recruitment or high oxygen inhalation despite proper positive end-expiratory pressure (F<sub>I</sub>O<sub>2</sub>) and refractory respiratory acidosis (PaCO<sub>2</sub> > 60 mmHg and/or pH < 7.20). The lung-protective CMV strategy was as follows: tidal volume, 6 mL/kg ideal body weight, platform pressure  $\leq 35$  cmH<sub>2</sub>O or upper inflection point value, and positive end-expiratory pressure set at 2 cmH<sub>2</sub>O above the lower inflection point. The patients were randomized prospectively (use of opaque closed envelope) and assigned to 1 of the following 2 ventilation methods: (1) HFOV-SP or (2) HFOV-PP. Due to the nature of the intervention, blinding the doctor was not possible.

### Ventilation Strategies

Both groups used the same HFOV strategy. SLE6000 high-frequency oscillatory ventilator (SLE, Croyden, UK) was applied periodically with HFOV at the following settings. MAP initially was set at 10-to-15 cmH<sub>2</sub>O and then gradually increased with steps of 1 cmH<sub>2</sub>O every 2-to-3 minutes until the oxygenation no longer improved. MAP then was decreased by 1 cmH<sub>2</sub>O every 2-to-3 minutes until TcSaO<sub>2</sub> decreased and then added 1-to-2 cmH<sub>2</sub>O on the basis of this MAP value. Other parameters include F<sub>I</sub>O<sub>2</sub>, 0.6; oscillation frequency, 8-to-12 Hz; percent inspiratory time, 33%; and initial amplitude, 30-to-40 cmH<sub>2</sub>O. Percutaneous carbon dioxide monitoring was used in the infants receiving HFOV. Oscillation amplitude was set to ensure that percutaneous carbon dioxide was stable within the target range (35-45 mmHg). After 1 hour of mechanical ventilation, ideal lung inflation was examined by chest radiography, and the right diaphragm generally was kept at the level of the ninth rib. All patients were sedated and paralyzed throughout the study period with continuous infusion of sufentanil, midazolam, and rocuronium bromide.

### Prone Position Strategy

The ventilator parameters remained unchanged for the infants in the HFOV-PP group. Before the body position was changed, the sputum was aspirated, and the gastric tube was sucked to expel gas in the stomach. Three staff members were assigned to prone position care. First, the infant was moved to the edge of the bed and turned to the opposite side to make the infant lie on his or her side. The hips and shoulders then were moved back until the prone position was reached. Various catheters and monitoring wires were positioned properly to assess changes in vital signs. The baby's head was laid sideways toward the ventilator, and rubber cushions were placed on the baby's shoulders and hip joints to ensure that the abdomen was suspended. The baby's hands were placed naturally on both sides of the body or head. Finally, changes in vital signs were observed closely during the prone position. The duration of treatment in the prone position was 12 hours, after which it was changed to the supine position. Criteria for the termination of prone position were as follows: cardiac arrest, obstruction of the large airway, prolapse or displacement of

tracheal intubation, mean arterial pressure <40 mmHg or systolic blood pressure drop of >20 mmHg, heart rate slow down <60 beats/min,  $F_{I}O_2 = 100\%$ ,  $SpO_2 <85\%$  or  $PaO_2 <50$  mmHg, barotrauma, pressure injury, or other situations in which the clinician decided to immediately stop.

### Definitions

The diagnosis of ARDS was based on the medical history, manifestations, and chest radiographs defined by the Pediatric Acute Lung Injury Consensus Conference Group in 2015.<sup>12</sup> Ventilator-related association was diagnosed according to the standards established by the Centers for Disease Control and Prevention with the aid of chest radiographs, professional training, effusions, transtracheal fluid, and clinical manifestations.<sup>13</sup> Diagnostic criteria for low-cardiac-output syndrome were blood pressure lower than the normal age-related values, central venous oxygen saturation value <30% of the arterial saturation, diuresis <1 mL/kg/h, peripheral temperature <32° C, and serum lactate >3 mmol/L.<sup>14</sup> Hypocarbica was defined as  $PaCO_2 <35$  mmHg, and hypercarbia was defined as  $PaCO_2 >60$  mmHg. Hypoxemia was defined as  $PaO_2 <50$  mmHg and/or  $PaO_2/F_{I}O_2 <200$  mmHg. Pediatric ARDS severity was defined using the oxygenation index (OI) ( $[F_{I}O_2 \times MAP \times 100] \div PaO_2$ ) and categorized as mild ( $4 \leq OI < 8$ ), moderate ( $8 \leq OI < 16$ ) or 7.5 or severe ( $OI \geq 16$ ).<sup>1</sup>

### Outcome Assessment

The primary outcomes were the  $PaO_2/F_{I}O_2$  ratio and OI at 1, 6, and 12 hours after intervention (T1, T6, T12); and the secondary outcomes were respiratory variables, hemodynamics, intervention safety, complications, and other short-term outcomes. Arterial blood gas was evaluated 30 minutes after the intervention, using a blood gas analyzer (ABLTM 900 radiometer, Copenhagen, Denmark), and every 4- to-6 hours or more often as needed. The infants were monitored using pulse oximetry, central venous pressure, and arterial blood pressure measurements. Data from the ventilator were exported into a spreadsheet for analysis.

### Statistical Analysis

The sample size calculation was based on the improvement of the  $PaO_2/F_{I}O_2$  ratio in the prestudy, using the PASS software (version 15; NCSS LLC, Kaysville, UT) after the 12-hour intervention. Assuming that the difference between the 2 groups was 20%, take  $\alpha = 0.05$ ,  $\beta = 0.2$ , considering the 1:1 distribution rate and the 20% dropout rate, each group (HFOV-SP and HFOV-PP) needed to include at least 29 patients.

An intention-to-treat analysis was performed. All statistics were conducted using SPSS software version 25.0 for Windows (SPSS, Chicago, IL). Data were expressed as mean  $\pm$  SD or median with an interquartile range according to their distribution. Independent continuous variables were presented as mean  $\pm$  SD and analyzed by *t*-tests. Categorical variables

were examined by the chi-square or Fisher exact test. The Mann-Whitney *U*-test was applied for nonnormally distributed data. All cytokine samples were analyzed in duplicate by laboratory staff who were blinded to the ventilation strategy, and communicated the results to the investigator at the end of the analysis. A *p* value < 0.05 indicated significance.

## Results

### Patient Characteristics

Among the 71 patients with ARDS admitted to the participating CICU from January 2020 to July 2021, 3 did not meet the inclusion criteria, and 3 parents of infants declined to participate. Finally, 65 infants were enrolled and completed the trial (32 in HFOV-PP group; 33 in HFOV-SP group) (Fig. 1). The main clinical characteristics, including sex, age, weight, ARDS severity, surgical data, perioperative status, and CHD type, were similar between the groups (*p* > 0.05) (Table 1). After an average of  $22.5 \pm 5.3$  postoperative hours, the patients were placed in the prone position for 12 hours. The ventilatory settings were similar between the groups (Table 2). These results indicated that the 2 groups of patients were homogeneous and comparable.

### Primary Outcomes

#### Oxygenation

Oxygenation was improved after HFOV in both groups (Figs. 2 and 3). However, the  $PaO_2/F_{I}O_2$  ratio and OI were more pronounced in the HFOV-PP group at T1, T6, and T12 after the intervention (*p* < 0.05). Detailed data regarding the  $PaO_2/F_{I}O_2$  ratio and OI changes during the experimental period are displayed in Figs. 2 and 3.

### Secondary Outcomes

#### Respiratory Variables and Hemodynamics

$PaO_2$  was improved after HFOV support in both groups. Particularly, the improvement in the HFOV-PP group was more statistically significant than that in the HFOV-SP group (*p* < 0.05) (Table 2). The MAP and  $F_{I}O_2$  in both groups decreased gradually after HFOV intervention. At T6 and T12, the MAP and  $F_{I}O_2$  in the HFOV-PP group were significantly lower than those in the HFOV-SP group (*p* < 0.05). The frequency and amplitude of the ventilator during the study period did not differ significantly between the 2 groups (Table 2). No significant changes in  $PaCO_2$  and diffusion coefficient of  $CO_2$  were observed between the 2 groups throughout the study period (Table 2). All infants in the 2 groups were hemodynamically stable (Table 3). Compared with that at T0, the central venous pressure of the 2 groups began to increase from T1 to T12 (Table 3). No significant differences in MAP, heart rate, cardiac index, and vasoactive-inotropic score were found between the 2 groups (Table 3).

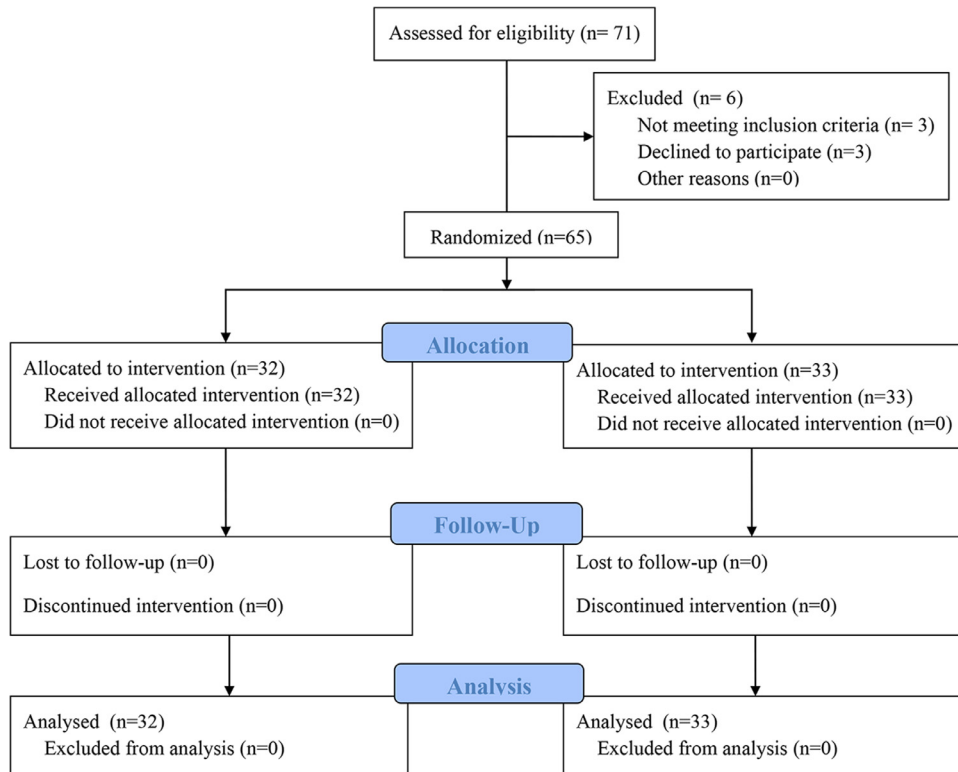


Fig 1. Participants' CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

### Complications and Short-Term Outcomes

No cardiovascular or pulmonary complications were noted during the study period. No serious complications related to the prone position occurred, and no accidental extubation or accidental removal of the peripheral venous catheter and reflux

of enteral feeding substance were recorded. One patient in the prone position group developed a slight pressure ulcer on the face but recovered 3 days after symptomatic management. Another patient in the prone position group developed ductus arteriosus displacement. Compared with those in the HFOV-SP, the duration of invasive ventilation and length of CICU

Table 1  
Clinical Characteristics of Included Patients\*

Characteristics	HFOV-PP (n = 32)	HFOV-SP (n = 33)	p Value
Sex, male/female patients	17/15	19/14	0.805
Age at surgery, mean $\pm$ SD, d	68.5 $\pm$ 11.3	72.5 $\pm$ 9.3	0.122
Weight at surgery, mean $\pm$ SD, kg	5.0 $\pm$ 0.6	4.9 $\pm$ 0.9	0.320
Preoperative respiratory failure, n (%)	9 (28)	7 (21)	0.574
Preoperative pulmonary hypertension, n (%)	9 (28)	13 (39)	0.434
Pulmonary surfactant, n (%)	2 (6)	4 (13)	0.672
OI at inclusion	12.7 $\pm$ 5.2	13.6 $\pm$ 4.0	0.486
PaO <sub>2</sub> /F <sub>I</sub> O <sub>2</sub> at inclusion	132.5 $\pm$ 29.5	140.8 $\pm$ 28.1	0.256
Congenital heart disease			
VSD	6	9	
TAPVC	6	7	0.982
COA	5	4	
PDA	5	4	
TGA	4	4	
VSD + ASD	3	3	
IAA	3	2	
CPB time, mean $\pm$ SD, min	114.2 $\pm$ 25.8	115.5 $\pm$ 29.0	0.836
Aortic cross-clamp time, mean $\pm$ SD, min	56.7 $\pm$ 19.5	53.4 $\pm$ 22.0	0.520

Abbreviations: ASD, atrial septal defect; COA, coarctation of the aorta; CPB, cardiopulmonary bypass; F<sub>I</sub>O<sub>2</sub>, fraction of inspired oxygen; HFOV, high-frequency oscillation ventilation; IAA, interrupted aortic arch; OI, oxygenation index; PaO<sub>2</sub>, partial pressure of oxygen; PDA, patent ductus arteriosus; PP, prone position; SP, supine position; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; VSD, ventricular septal defect.

\* Data reported as number and percentage or mean  $\pm$  SD.

Table 2  
Ventilation and Respiratory Variables During the Trial Periods\*

Variable	Group	T0	T1	T6	T12
MAP, cmH <sub>2</sub> O	HFOV-SP	19 ± 3	18 ± 6	19 ± 4 <sup>†</sup>	17 ± 5 <sup>†</sup>
	HFOV-PP	18 ± 4	17 ± 3	15 ± 3 <sup>†</sup>	14 ± 4 <sup>†</sup>
Amplitude, mbar	HFOV-SP	33 ± 4	29 ± 3	30 ± 5	31 ± 4
	HFOV-PP	31 ± 5	30 ± 3	30 ± 5	29 ± 3
F <sub>I</sub> O <sub>2</sub> , %	HFOV-SP	70 ± 11	68 ± 8	65 ± 7 <sup>†</sup>	64 ± 9 <sup>†</sup>
	HFOV-PP	72 ± 8	65 ± 7	55 ± 5 <sup>†</sup>	50 ± 8 <sup>†</sup>
Frequency, Hz	HFOV-SP	9.5 ± 1.5	9.5 ± 1.5	9.5 ± 1.5	9.5 ± 1.5
	HFOV-PP	10.0 ± 1.0	10.0 ± 1.0	10.0 ± 1.0	10.0 ± 1.0
DCO <sub>2</sub> , mL <sup>2</sup> /s	HFOV-SP	905.1 ± 167.3	920.3 ± 144.8	951.2 ± 171.4	968.8 ± 157.8
	HFOV-PP	885.7 ± 187.5	955.5 ± 165.7	980.3 ± 158.3	995.8 ± 177.5
PO <sub>2</sub> , mmHg	HFOV-SP	63.5 ± 19.2	68.7 ± 10.5 <sup>†</sup>	76.7 ± 15.5 <sup>†</sup>	87.5 ± 15.6 <sup>†</sup>
	HFOV-PP	61.5 ± 16.1	81.2 ± 13.4 <sup>†</sup>	93.5 ± 17.6 <sup>†</sup>	110.4 ± 22.5 <sup>†</sup>
PCO <sub>2</sub> , mmHg	HFOV-SP	46.5 ± 7.1	42.2 ± 9.0	45.1 ± 7.3	48.2 ± 6.0
	HFOV-PP	47.3 ± 6.6	42.0 ± 7.6	39.3 ± 6.3	40.5 ± 7.1

Abbreviations: DCO<sub>2</sub>, diffusion coefficient of CO<sub>2</sub>; F<sub>I</sub>O<sub>2</sub>, fraction of inspired oxygen; HFOV, high-frequency oscillation ventilation; MAP, Mean airway pressure; PCO<sub>2</sub>, partial pressure of carbon dioxide; PO<sub>2</sub>, partial pressure of oxygen; PP, prone position; SP, supine position; T0, immediately after the intervention; T1, 1 hour after the intervention; T6, 6 hours after the intervention; T12, 12 hours after the intervention.

\*Data are presented as mean ± SD.

† Indicates that there is a significant difference between the 2 groups, and the p value is < 0.05.

stay were shorter in the HFOV-PP group ( $p < 0.05$ ). No significant differences in pneumothorax, ventilation-associated pneumonia, in-hospital mortality, and total hospital length of stay were found between the 2 groups ( $p > 0.05$ ) (Table 4).

## Discussion

This study was the first to investigate the application of HFOV-PP in infants with ARDS after congenital heart surgery through a prospective randomized controlled trial, and demonstrated that HFOV-PP can significantly improve oxygenation in infants with ARDS, and also showed that the therapy is safe after thoracotomy.

After cardiac surgery, the inflammation caused by cardiopulmonary bypass, thoracotomy, and ischemia-reperfusion injury, and the postoperative gravitational forces of the heart and mediastinum on nearby pulmonary segments, are closely related to the occurrence of ARDS after surgery for CHD.<sup>15</sup> Human and animal model studies have confirmed the efficacy of the prone position and/or HFOV on ARDS.<sup>7,16-19</sup> Martinsson et al found that the prone position, combined with the recruitment maneuver for cardiac surgery patients, can improve lung ventilation and oxygenation and shorten the time of oxygen therapy after extubation.<sup>17</sup> Bojan et al found that the early postoperative application of HFOV can shorten the duration of mechanical ventilation and intensive care unit

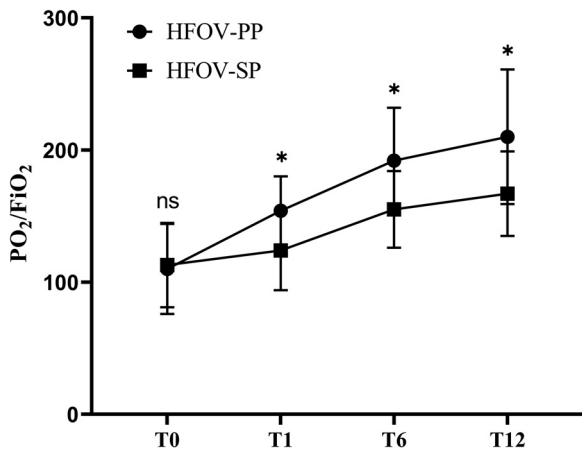


Fig 2. Evolution of PaO<sub>2</sub>/F<sub>I</sub>O<sub>2</sub> ratio at T0, T1, T6, and T12 of the study. HFOV, high-frequency oscillatory ventilation; ns, not significant; PP, prone position; SP, supine position; T0, immediately after the intervention; T1, 1 hour after the intervention; T6, 6 hours after the intervention; T12, 12 hours after the intervention.

\*The difference between the 2 groups was statistically significant; data expressed as mean ± SD.

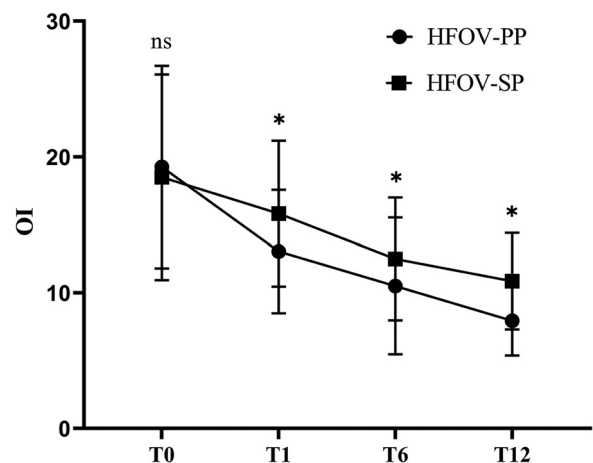


Fig 3. Evolution of OI at T0, T1, T6, and T12 of the study. HFOV, high-frequency oscillatory ventilation; ns, not significant; OI, oxygenation index; PP, prone position; SP, supine position; T0, immediately after the intervention; T1, 1 hour after the intervention; T6, 6 hours after the intervention; T12, 12 hours after the intervention.\*The difference between the 2 groups was statistically significant; data expressed as mean ± SD.

Table 3  
Hemodynamic Parameters During the Trial Period\*

Variable	Group	T0	T1	T6	T12
HR, beats/min	HFOV-SP	135 ± 13	130 ± 11	129 ± 9	128 ± 12
	HFOV-PP	130 ± 15	135 ± 10	126 ± 11	131 ± 15
MAP, mmHg	HFOV-SP	71 ± 9	79 ± 8	82 ± 10	83 ± 8
	HFOV-PP	77 ± 11	83 ± 10	75 ± 12	80 ± 11
CVP, mmHg	HFOV-SP	9 ± 3	11 ± 5	12 ± 4	12 ± 5
	HFOV-PP	9 ± 4	12 ± 5	12 ± 6	10 ± 5
VIS	HFOV-SP	20 ± 6	18 ± 5	19 ± 7	18 ± 5.0
	HFOV-PP	18 ± 6	18 ± 6	17 ± 6	17 ± 5

Abbreviations: CVP, central venous pressure; HFOV, high-frequency oscillation ventilation; HR, heart rate; MAP, mean arterial pressure; PP, prone position; SP, supine position; T0, immediately after the intervention; T1, 1 hour after the intervention; T6, 6 hours after the intervention; T12, 12 hours after the intervention; VIS, vasoactive-inotropic score.

\* Data are presented as mean ± SD.

(ICU) stay for respiratory distress after congenital heart surgery.<sup>20</sup> However, the application of the prone position, combined with HFOV therapy in patients with postoperative hypoxemia of CHD, has not been reported. This study was the first to reveal the superiority of the combination of HFOV and the prone position in infants after cardiac surgery. Additionally, no serious complications occurred when the patients were moved to the prone position with proper care.

Forty years ago, the prone position was proposed to improve oxygenation in patients with hypoxic acute respiratory failure under mechanical ventilation.<sup>21</sup> The prone position is a rescue treatment for life-threatening hypoxemia. The mechanisms for improving oxygenation in the prone position mainly include the redistribution of lung density, recruitment of dorsal regions, increased chest wall elasticity, reduced alveolar shunt, enhanced ventilation-perfusion ratio, improved oxygenation and CO<sub>2</sub> clearance, decreased ventilator-induced lung injury, and cardiac response directing the pressure exerted by the heart on the lungs toward the sternum and, thus, reversing right-heart failure.<sup>22-24</sup> Most patients develop basal and dorsal atelectasis after cardiac surgery due to the inflammatory

Table 4  
Complications and Short-Term Outcomes\*

Variable	HFOV-PP (n = 32)	HFOV-SP (n = 33)	p Value
Pressure ulcer, n (%)	1	0	/
Artery catheter displacement, n (%)	1	0	/
Pneumothorax, n (%)	1 (3.1)	2 (6.1)	1.000
Ventilation-associated pneumonia, n (%)	5 (15.6)	4 (12.1)	1.000
In-hospital mortality, n (%)	0	1 (3.0)	/
Duration of invasive ventilation, mean ± SD, d	5.2 ± 2.0	7.8 ± 3.1	0.004
CICU length of stay, mean ± SD, d	8.8 ± 2.4	12.2 ± 4.3	0.039
Total hospital length of stay, mean ± SD, d	16.3 ± 4.0	19.5 ± 3.5	0.606

Abbreviations: CICU, cardiac intensive care unit; HFOV, high-frequency oscillatory ventilation; PP, prone position; SP, supine position.

\* Data reported as number and percentage or mean ± SD.

effects of cardiopulmonary bypass, thoracotomy, and ischemia-perfusion injury;<sup>25-26</sup> the gravity amplification of the heart and mediastinum in the nearby lung segment after surgery; and the lung becoming fragile and prone to atelectasis after cardiac surgery.<sup>15</sup> Brussel et al found that in patients with acute respiratory failure after cardiac surgery, prone positioning can reduce atelectasis and improve oxygenation due to the redistribution of ventilation from the ventral and apical areas, consequently improving the dorsal ventilation-perfusion ratio.<sup>27</sup> The present study also found that compared with HFOV-SP, HFOV-PP significantly improved oxygenation and shortened the duration of postoperative invasive mechanical ventilation. Although the prognosis improvement of patients with ARDS after PP treatment is not related to the increased oxygenation, postoperative oxygenation improvement for patients after cardiac surgery can lead to early extubation and a shortened length of ICU stay.<sup>28</sup>

Lung-protective mechanical ventilation strategy with low tidal volume is one of the cornerstones of ARDS management.<sup>29</sup> Theoretically, HFOV applies tidal volume less than or equal to the anatomic deadspace, low periodic pressure changes, and high physiologic respiratory frequency oscillations, and then achieves the alveolar ventilation mode of rapid gas exchange. Additionally, HFOV is active in inhalation and exhalation during ventilation, which can uniformly expand the alveoli in a short time without increasing barotrauma, thereby effectively improving oxygenation and carbon dioxide emissions.<sup>30-31</sup> Bojan et al found that compared with CMV, the application of HFOV in infants with respiratory distress after cardiac surgery can shorten the time of mechanical ventilation and ICU hospitalization.<sup>20</sup> However, controversies still surround the clinical application of HFOV. Gupta et al analyzed the data of the virtual pediatric ICU database and found that compared with those under CMV, the patients treated with HFOV had increased mortality and morbidity and a significantly longer time spent on the ventilator; this finding poses a challenge to the use of HFOV.<sup>32</sup> As a new type of ventilation, the safety and effectiveness of HFOV in ARDS must be studied further.

HFOV and PP have been proposed as alternative strategies to CMV, especially in patients with severe hypoxemia, because of their dual potential to improve gas exchange and prevent ventilator-induced lung injury development.<sup>6,33</sup> However, their combination has not been widely explored. In this study, the authors found that HFOV-PP significantly increased oxygenation compared with HFOV-SP due to the continuous high MAP during HFOV that can simultaneously open slow-recruiting compartments and the fast-collapsing portions of the lungs.<sup>34</sup> In the prone position, oxygenation can be improved by homogenizing the ventral and dorsal distribution of ventilation, thereby improving ventilation in the dorsal lung area.<sup>18</sup> Therefore, HFOV and the prone position exhibit a synergistic, at least additive, effect in terms of gas exchange.

Ventilation in a prone position also has some complications, such as endotracheal tube displacement, tracheal tube obstruction or bending, artery catheter displacement, and pressure ulcers. In this study, the authors found 1 case of pressure ulcer

in the HFOV-PP ventilation group. Another infant had an accidental removal of the arterial catheter. Therefore, corresponding measures should be taken to prevent these complications during PP ventilation.<sup>34</sup> Furthermore, compared with other previous studies,<sup>19,35</sup> the mortality rate of ARDS after congenital heart surgery was lower in this study, which may have been due to the relatively mild lung injury and small sample size of the infants included in this study.

### Limitations

This study was the first clinical trial using HFOV-PP in infants with ARDS after congenital cardiac surgery. However, several limitations must be addressed. Firstly, this randomized controlled research was not a double-blind study; some subjective indicators were included in the research evaluation criteria. Secondly, this trial was a single-center study with a relatively small sample size and a short observation time. Additionally, the investigation was limited to infants undergoing cardiac surgery; other patients might have different results. Future studies must be conducted to clarify whether the new strategy of HFOV-PP has a beneficial effect on the oxygenation and prognosis of patients after cardiac surgery.

### Conclusions

HFOV, combined with PP, is a safe and feasible treatment of ARDS after cardiac surgery and can effectively improve oxygenation. Multicenter and large-sample studies are needed to confirm this finding.

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### Conflict of Interest

None.

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