Effect of high frequency oscillatory ventilation combined with pulmonary surfactant in the treatment of acute respiratory distress syndrome after cardiac surgery: a prospective randomized controlled trail

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Abstract

Objective: This study aimed to evaluate the effects of pulmonary surfactant (PS) combined with high-frequency oscillatory ventilation (HFOV) or conventional mechanical ventilation (CMV) in infants with acute respiratory distress syndrome (ARDS) after congenital cardiac surgery.

Method: A total of 61 infants with ARDS were eligible and were randomized to the CMV + PS group (n= 30) or the HFOV + PS group (n= 31) between January 2020 and December 2020. The primary outcomes were the improvement of the arterial blood gas analysis. The incidence of mechanical ventilation duration, length of hospitalization, and the incidence of complications were considered as secondary outcomes.

Results: A total of 61 infants completed the study. In HFOV + PS group, the blood gas analysis results were significantly improved ($P<0.05$), while, duration of mechanical ventilation and length of hospitalization were shorter than CMV + PS group ($P<0.05$). But the incidences of complications had no statistical significance between the two groups ($P>0.05$).

Conclusions: Compared with the CMV + PS group, HFOV + PS significantly improved the ABG variables and shortened the length of hospitalization and mechanical ventilation in infants with ARDS after cardiac surgery.

Introduction

With the continuous improvement of cardiopulmonary bypass technology, the safety of surgical correction of congenital heart disease (CHD) has increased, but acute lung injury and acute respiratory distress syndrome (ARDS) often occur after cardiopulmonary bypass (CPB). It is reported that up to 20% of cardiac surgery patients will develop ARDS during the perioperative period, and the mortality rate is as high as 80%[1,2]. The systemic inflammatory response and lung ischemia-reperfusion injury caused by CPB during cardiac surgery are related to ARDS[3,4]; The cornerstone of ALI/ARDS management is lung-protective mechanical ventilation with low tidal volumes[5]. Among them, high-frequency oscillatory ventilation (HFOV) applies tidal volume less than or equal to the anatomical dead space for rapid gas exchange has been proven to be a protective effect on the lungs[6,7]. Additionally, the application of exogenous pulmonary surfactant (PS) replacement therapy in neonatal respiratory distress syndrome (NRDS) has been popularized, and the curative effect has been determined. However, the effect of pediatric ARDS needs to be further studied[1,8]. HFOV + PS inhalation therapy has achieved good results in the treatment of various respiratory diseases in newborns and infants, such as NRDS, congenital diaphragmatic hernia and meconium aspiration syndrome[9,10]. However, the research of HFOV + PS on the treatment of secondary ARDS after cardiac surgery in infants is still limited. The purpose of this study is to evaluate the efficacy and safety of HFOV + PS versus CMV + PS in the treatment of ARDS after cardiac surgery.

Materials And Methods

Population and study criteria

This was a single-center, prospective randomized controlled study conducted in the cardiac intensive care unit (CICU) from January 2020 to December 2020 at a provincial hospital in China. The trial was approved by the ethics committee of Fujian Maternity and Child Health Hospital (NO. 2020YJ181) and adhered to the tenets of the Declaration of Helsinki (as revised in 2013). Informed parental written consent from all subjects were obtained.

The inclusion criteria were as follows: 1. Infants were suffering from ARDS in our CICU. 2. The patient's anatomical treatment was satisfactory, cardiac function recovered well after the operation, and hemodynamics was stable. The exclusion criteria included hemodynamically significant residual lesions, pulmonary venous obstruction, parents' decision not to participate.

Allocation

After documenting parental consent, all infants were assigned using a table of computer-generated random numbers and sealed opaque envelopes to either HFOV + PS or CMV + PS.

Respiratory management

Pulmonary surfactant (PS): The PS (porcine surfactant, Curosurf®, Chiesi Pharmaceutical SpA, Parma, Italy) was used for intratracheal injection. The infants in both groups were given a dose of 100 mg/kg in one dose within 6 h after ARDS diagnosis. Before application, the airway secretions were aspirated, and the circulation was maintained stable to correct the acid-base disorder. After PS injection, pressurize and ventilate rapidly for 1 min, then connect to a ventilator to maintain HFOV/CMV ventilation.

Mechanical ventilation: HFOV+PS group: High frequency oscillating ventilator (SLE 5000, SLE UK, Croyden, United Kingdom) was used for mechanical ventilation before PS application. The ventilator's initial parameters were as follows: a frequency of 8-12 Hz and an inspiratory: expiratory ratio of 1:1 were used in each case; The mean airway pressure (MAP) was initially set at 10-15 cmH$_2$O and then gradually increased with steps of 1 cmH$_2$O every 2–3 min until the oxygenation no longer improved or the FiO$_2$ was ≤ 0.40; Then, the MAP was decreased by 1–2 cmH$_2$O every 2–3 min until FiO$_2$ began to rise again. The amplitude was initially set at 30-40 cmH$_2$O. After one hour of mechanical ventilation, ideal lung inflation was examined by chest radiography, and the right diaphragm was generally kept at the level of the ninth rib. The parameter adjustment is determined according to the results of the dynamic monitoring of blood gas analysis. After continuous ventilation for at least 10 minutes, PS was injected through the tracheal tube. The changes in oxygen saturation (SaO$_2$), heart rate, respiration, and blood pressure were closely monitored during the treatment. If the infant suffered from apnea, SaO$_2$ or the heart rate dropped, the injection was suspended and oxygen was rapidly pressurized until the stable state was restored. After PS was applied, mechanical ventilation was continued, and the ventilator parameters were readjusted

according to the results of SaO_2, blood gas analysis and chest radiograph. Infants were extubated when they achieved the following criteria: hemodynamic stability, MAP < 8 cmH$_2$O, FiO$_2$ < 40%, and weaned sedation. The infants were transferred to conventional ventilation before extubation. After weaning, nasal continuous positive pressure ventilation (NCPAP) was administered through a nasal interface.

CMV+PS group: The Stephanie ventilator (Fritz Stephan GmbH, Gackenbach, Germany) was used for CMV. The initial parameters: FiO$_2$: 30%~50%, PIP: 18-25cmH$_2$O, PEEP: 4~6 cmH$_2$O, I/E: 1-1.5:1, RR: 30~40 times/min. According to the results of SaO$_2$, arterial blood gas (ABG) analysis and chest radiograph, the parameters of the ventilator were adjusted, and continuous positive pressure ventilation (NCPAP) was given through nasal congestion after weaning.

Definitions and data collection

Outcome measures: The ventilatory settings, ABG analysis, oxygenation index (OI), duration of mechanical ventilation, and complications of ventilation were recorded during the study period. The primary outcome was short term oxygenation, and the secondary outcome was the duration of mechanical ventilation and length of hospitalization. The diagnosis of ARDS was established according to the medical history, clinical manifestations, and chest radiograph results which defined in 2015 by the Pediatric Acute Lung Injury Consensus Conference Group (PALCCG)[1], and met the following conditions: (1) hypoxemia with OI ≥ 4 or oxygenation saturation index (OSI) ≥ 5; (2) new radiological lung infiltrates; (3) occurred within 7 days of a known clinical insult; and (4) could not be explained by cardiac failure or fluid overload. (5) other patients with chronic lung/heart diseases, such as cyanotic heart disease, chronic lung disease, and left ventricular dysfunction to be included as long as they fulfilled the criteria above and the acute deterioration in oxygenation and pulmonary infiltrates could not be explained by their pre-existing diseases. (6) excluded patients with perinatal related lung disease. The diagnosis of ventilator-associated pneumonia (VAP) was based on the criteria established by the Centers for Disease Control and Prevention, with diagnosis aided by chest radiographs, positive sputum cultures, transtracheal fluid, bronchial washings, and clinical findings[11]. A diagnosis of VAP was considered when it was identified after 48 hours of mechanical ventilation. We analyzed demographics and clinical characteristics, surgical and CPB techniques, radiology and laboratory test results, ABG analysis, short-term outcomes, such as VAP, sepsis, length of mechanical ventilation, length of ICU stay and in-hospital mortality. ABG analysis was evaluated 30 minutes after HFOV was started using a blood gas analyzer (ABLTM 700 radiometer, Copenhagen, Denmark) and repeated every 4-6 hours or more often as needed. We elected to use OI ([FiO$_2$ × mean airway pressure ×100] ÷ PaO$_2$) to define the severity of PARDS. The severity of ARDS was defined as follows: mild 4 ≤ OI < 8, moderate 8 ≤ OI < 16 or 7.5, severe OI ≥ 16.[1]

Statistical analysis

Based on the improvement of the ABG in the pre-experiment, assuming the difference between the two independent populations was 15%, α=0.05, and β=0.2, the number of participants needed was 27 in each group. Assuming a 10% attrition rate, the total sample size was 60 (30 per group).

Data were analyzed using 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 nonnormally distributed data. A two-sided P-value of <0.05 was regarded as statistically significant.

Results

Baseline data

A total of 65 infants were screened between January 2020 and December 2020, of which 2 did not meet inclusion criteria, 2 parents of infants declined to participate. Finally, and 61 infants were ultimately enrolled and finished the trial (31 in HFOV + PS group; 30 in CMV + PS group) (Fig. 1). There were no significant differences in main clinical characteristics including gender, GA, weight, the severity of ARDS or surgical data (Table 1). These results indicated that the two groups of patients were homogeneous and comparable.

Table 1
Baseline characteristics a.

Characteristics	HFOV + PS (n = 31)	CMV + PS (n = 30)	P-Value
Sex (Male/Female)	19/12	17/13	0.797
Gestation age at birth (weeks; mean ± SD)	38.2 ± 2.1	38.0 ± 2.2	0.658
Age at surgery (days; mean ± SD)	50.3 ± 15.7	46.7 ± 14.7	0.397
Weight at surgery (kg; mean ± SD)	4.3 ± 0.7	4.5 ± 0.8	0.406
Preoperative respiratory failure, n (%)	11 (35.5)	9 (30)	0.786
Pulmonary hypertension, n (%)	20 (64.5)	23 (76.7)	0.402
Operation time (h; mean ± SD)	3.8 ± 0.8	3.5 ± 1.1	0.319
CPB time (h; mean ± SD)	2.1 ± 0.3	2.0 ± 0.5	0.299
Severity of ARDS, n			
Mild	10	8	
Moderate	17	20	
Severe	4	2	
Congenital heart disease, n			
VSD	17	20	
ASD	6	3	
PDA	3	2	
COA	1	1	
TAPVC	2	1	
PA	1	1	
IAA	1	2	

Abbreviations: CPB: cardiopulmonary bypass; ARDS: acute respiratory distress syndrome; VSD: ventricular septal defect; ASD: atrial septal defect; PDA: patent ductus arteriosus; COA: coarctation of aorta; TAPVC: total anomalous pulmonary venous connection; PA: pulmonary atresia; IAA: interrupted aortic arch.

a: Data reported as number and percentage, mean + standard deviation.

Primary outcomes: ABG analysis results

There was no statistically significant difference in arterial partial pressure oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), PaO_2/FiO_2, and OI between the two groups of children at the beginning of treatment (P > 0.05). After 6h, 12h, 24h and 48h of mechanical ventilation treatment, the blood gas analysis results were significantly improved and the difference was statistically significant (P < 0.05). (Fig. 2).

Secondary outcomes: treatment efficacy and complications.

During the application of HFOV + PS treatment, it was found that the heart rate decreased slightly (134 ± 17 vs. 143 ± 20 beats/min), whereas mean arterial pressure (79 ± 14 vs. 83 ± 10 mmHg) and inotropic score (17.0 ± 5.5 vs. 16.0 ± 6.3) remained stable during this period, and the difference was statistically significant. The length of hospital stay between the two groups of infants and the CICU length of stay in the HFOV + PS group was significantly shorter than that in the CMV + PS group (*P* < 0.05). The duration of mechanical ventilation in the HFOV + PS group was also considerably shorter than that in the CMV + PS group (*P* = 0.03). There was no significant difference between the two groups in pneumothorax, VAP, sepsis, pulmonary hemorrhage, and in-hospital mortality (*P* > 0.05) (Table 2).

Table 2
Vital signs and complications of the study infants[a].

Variable	HFOV + PS (n = 31)	CMV + PS (n = 30)	P Value
Mean heart rate (beats/min, mean ± SD)	134 ± 17	143 ± 20	0.052
Mean arterial pressure, mean ± SD	79 ± 14	83 ± 10	0.110
Mean inotropic score (24 hours postoperatively), mean ± SD	17.0 ± 5.5	16.0 ± 6.3	0.156
VAP, n (%)	4 (12.9)	2 (6.7)	0.671
Sepsis, n (%)	3 (9.7)	4 (13.3)	0.707
Pulmonary hemorrhage, n (%)	1 (3.2)	3 (10)	0.354
Pneumothorax, n (%)	0	2 (6.7)	0.492
In-hospital Mortality, n (%)	1 (3.2)	3 (10)	0.354
Postoperative duration of intubation (days; mean ± SD)	6.6 ± 2.8	8.7 ± 4.4	**0.030**
CICU length of stay (days; mean ± SD)	11.2 ± 4.5	14.1 ± 3.3	**0.006**
Total hospital length of stay (days; mean ± SD)	19.9 ± 2.9	21.7 ± 3.0	**0.032**
Abbreviations: VAP, ventilator-associated pneumonia; CICU, cardiac intensive care unit;			
[a]Data reported as number and percentage, mean ± standard deviation.			

Discussion

ARDS is a serious complication after cardiac surgery in children. The main manifestations are the increase in extensive alveolar permeability and refractory hypoxemia. Hypoxia and acidosis damage pulmonary vascular endothelial cells and alveolar epithelial cells. Increased pulmonary microvascular permeability leads to alveolar and pulmonary interstitial edema, damages alveolar type Ⅱ cells, and leads to decreased production or release of endogenous PS, decreased activity, and alveolar surface tension increases and lung compliance decreases, leading to impaired lung function and decreased oxygenation levels[12,13]. Hypoxia and acidosis will affect hemodynamics in the short term, aggravate the degree of low cardiac output, and even cause multiple organ failure. Mechanical ventilation is the most important treatment. However, studies have found that conventional mechanical ventilation itself can also cause and aggravate lung damage, mainly due to high airway pressure, high lung volume, and repeated opening and closing of collapsed alveoli, which can trigger the release of inflammatory factors and secondary multiple organ dysfunction[14]. Therefore, the lung-protective ventilation strategy has become the key to

mechanical ventilation, among which the two most important aspects are limiting the excessive expansion of alveoli through neaps and applying relatively high PEEP to avoid the repeated closure of end-expiratory alveoli, thus reducing lung injury and promoting disease recovery.

HFOV generates biphasic pressure changes with a tidal volume less than or equal to the anatomic dead space, low periodic pressure changes and hyperphysiological respiratory frequency oscillations, and then achieves an alveolar ventilation mode of effective gas exchange, which can uniformly expand alveoli in a short time and improve gas exchange and lung compliance. HFOV is active in inhalation and exhalation during ventilation, effectively improving oxygenation and carbon dioxide emission without increasing barotrauma. Its hypoventilation strategy can prevent lung injury during mechanical ventilation and improve survival rate[15,16]. Poddutoor et al.[17] conducted a study on 675 neonates receiving CMV, and found that 97 cases were changed to HFOV treatment after CMV treatment failed, and the pulmonary oxygenation function and ABGs were significantly improved after 2 hours. Our study also showed that the ABG results of the HFOV + PS group were significantly improved after treatment. Although the ABG results of the CMV + PS group were also improved, the effect was not as obvious as that of the HFOV + PS group. In addition, the average length of hospital stay and on-boarding time of infants in the HFOV + PS group were significantly shorter than those in the CMV + PS group. In addition, the length of hospitalization and the duration of mechanical ventilation in the HFOV + PS group were considerably shorter than those in the CMV + PS group. This was because, compared with CMV, the high-speed flow of gas produced by HFOV could quickly diffuse PS to the surface of the alveoli, reduced its surface tension, further expanded the alveoli, maintained their stability, improved the alveolar ventilation and ventilation function, and further relieved the symptoms of hypoxia and acidosis.

PS replacement therapy can reduce alveolar surface tension, prevent alveolar collapse at the end of expiratory, maintain functional residual capacity, stabilize alveolar pressure and reduce fluid leakage from capillaries to alveoli. At the same time, it can improve lung compliance and ventilation function and reduce ventilator parameters.[18,19] Studies have shown that early use of PS in ARDS children can shorten the duration of mechanical ventilation and oxygen use.[20,21] Additionally, PS combined with mechanical ventilation can significantly increase PaO_2 / FiO_2, decrease OI, and significantly improve the oxygenation function of ARDS children compared with simple mechanical ventilation[22,23].This study also showed that the duration of mechanical ventilation and oxygenation of the HFOV + PS group were significantly lower than those of the CMV + PS group. The mechanism may be that HFOV can open occluded small airways and alveoli, and the extremely fast ventilation frequency and unique gas exchange mode accelerate the uniform distribution of PS on alveolar walls. In addition. The immunomodulatory, biophysical and antibacterial properties of surfactants help to stabilize the alveoli and reduce alveolar-capillary edema, ultimately helping to improve lung function[23]. When PS is used in combination with HFOV, it can significantly improve breathing and reduce ventilation duration.

Our study found that when HFOV was used in combination with PS, the incidence of pulmonary hemorrhage, pneumothorax, VAP, intracranial hemorrhage, and mortality in the two groups was not

statistically significant. The safety of HFOV has always been a concern by scholars. Studies have found that the incidence of chronic lung disease and mortality after the application of HFOV is slightly superior to that of CMV, and there is no significant difference in the occurrence of complications such as air leakage and brain injury[24,25]. Current clinical studies have shown that although exogenous PS can improve pulmonary gas exchange in infants with ARDS, its effect on reducing the mortality rate is uncertain[26]. Clinical research should be continued to determine which types of ARDS is effective for PS, and the appropriate timing, dosage, and method of administration. Therefore, it is necessary to conduct a multicenter study to discuss related issues and provide evidence for the clinical use of exogenous PS in ARDS.

This is the first study using HFOV + PS in infants with ARDS after congenital cardiac surgery. However, there are several limitations to this study. First, this randomized controlled study was not a double-blind study; there were many subjective indicators in the research's evaluation criteria. Second, this was a single-center study with relatively small sample size. Finally, this study was limited to specific patients undergoing congenital cardiac surgery, and other patients might have different results. Therefore, more large-sample, multicenter, prospective, randomized, double-blind, and long-term studies are needed to determine the conclusions.

Conclusions

Compared with CMV + PS group, HFOV + PS can significantly improve the ABG variables and shorten the length of hospitalization and mechanical ventilation in infants with ARDS after cardiac surgery. Meanwhile, it does not increase the incidence of complications.

Declarations

Acknowledgments

Author contributions

Qiang Chen and Yirong Zheng conceived the idea; Hong-Lin Wu and Yu-Qing Lei conducted the analyses; Ning Xu and Shu-Ting Huang provided the data; all authors contributed to the writing and revisions.

Conflict of interest

The authors declare no conflicts of interest.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The ethics board of Fujian Medical University approved the study (NO. 2020KY039), and informed consent was taken from the patients' parents/guardians. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Informed consent

The informed consent was taken from the patients' parents/guardians.

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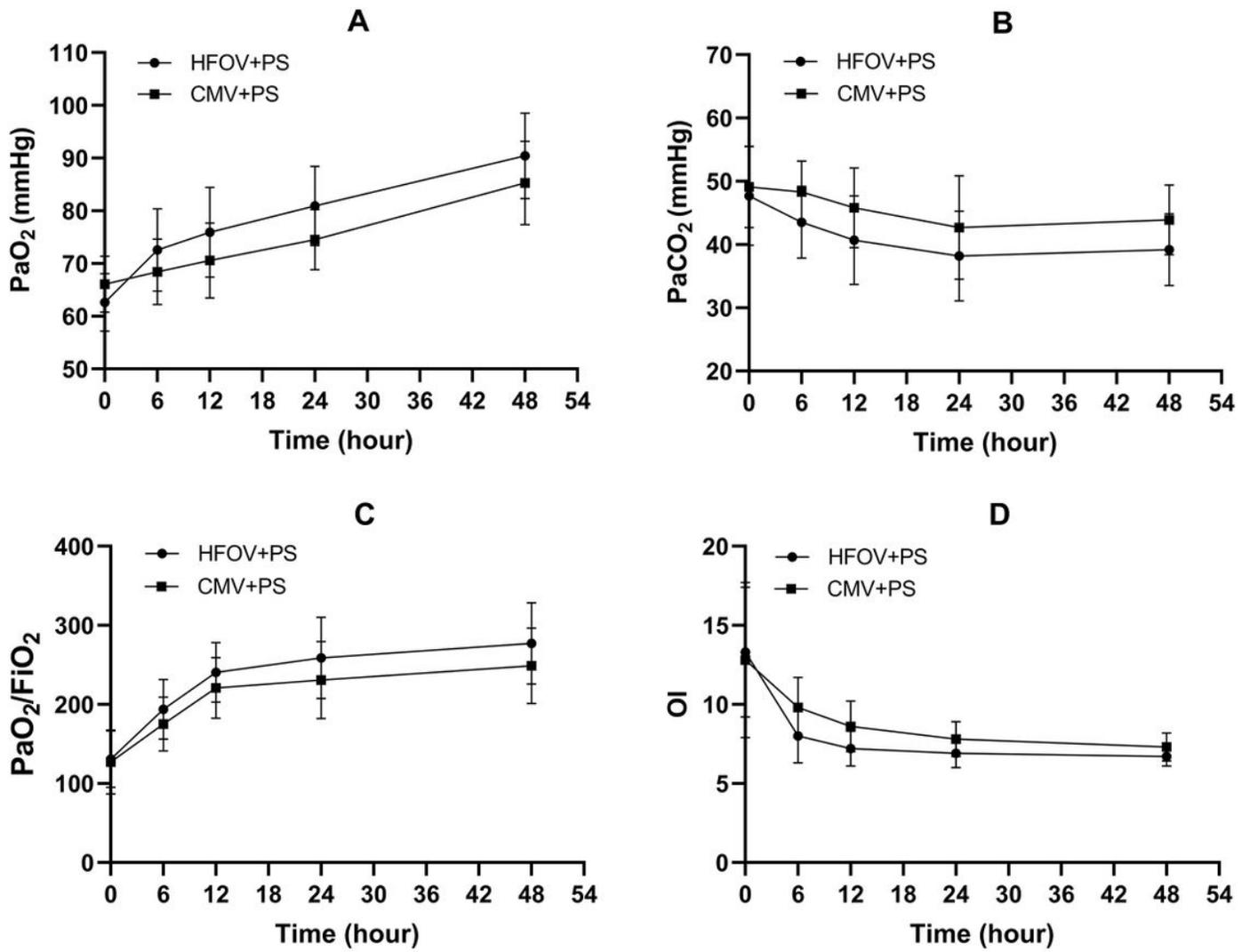
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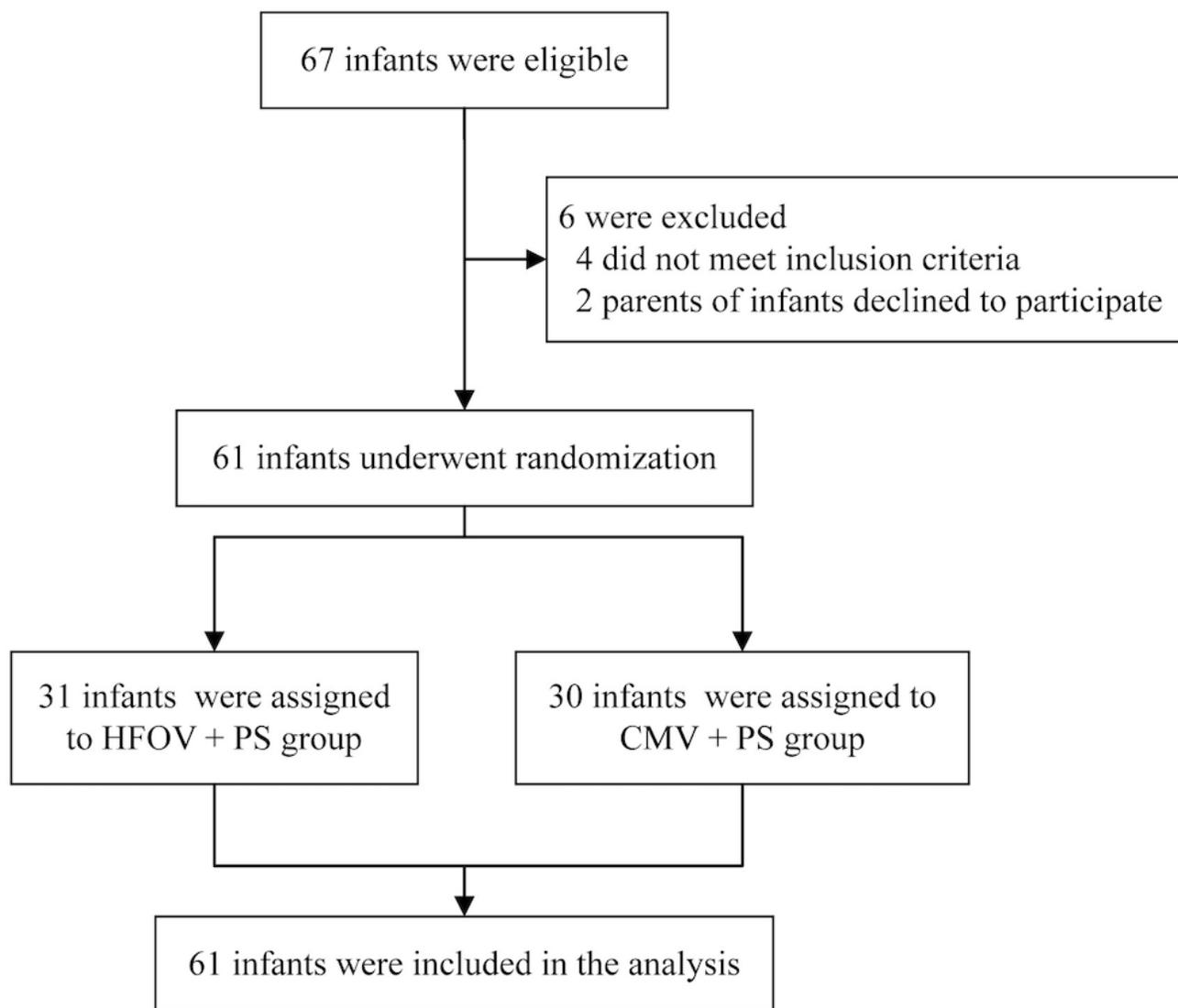
Figure 1

CONSORT flow diagram

Figure 2

Arterial blood gas analysis results