

## Original Article

# Comparison of efficacy of synchronized intermittent mandatory ventilation and invasive high-frequency oscillatory ventilation in neonatal respiratory failure and its effect on KL-6 and CC16 levels

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Received May 4, 2020; Accepted June 23, 2020; Epub September 15, 2020; Published September 30, 2020

**Abstract:** Objective: To compare the therapeutic efficacy of synchronous intermittent mandatory ventilation (SIMV) and invasive high-frequency oscillatory ventilation (i-HFOV) in neonatal respiratory failure (NRF) as well as its effect on KL-6 (surface antigen of alveolar type II) and CC16 (Clara cell protein) levels. Methods: The medical records of 113 neonates with respiratory failure in our hospital were collected retrospectively and divided into two groups based on the ventilation mode. Group A received SIMV, and group B received i-HFOV. Clinical efficacy, time on ventilator, oral feeding time, length of stay, adverse reactions, arterial blood oxygen partial pressure ( $\text{PaO}_2$ ), and partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) were compared. Respiratory index (RI) and oxygenation index (OI) were calculated, and serum levels of KL-6 and CC16 were measured by enzyme-linked immunosorbent assay. Results: The effective rate in group B was 92.98%, which was higher than 75.00% in group A ( $P < 0.05$ ). The time on ventilator, oral feeding time, and length of stay in group B were shorter than those in group A ( $P < 0.05$ ). The incidence of adverse reactions in group B was 7.02%, which was lower than 21.43% in group A ( $P < 0.05$ ). Compared with values at 0 h,  $\text{PaCO}_2$  decreased and  $\text{PaO}_2$  increased at 24 h and 72 h in both groups ( $P < 0.05$ ). Compared with group A, group B showed significantly lower  $\text{PaCO}_2$  and higher  $\text{PaO}_2$  at 24 h and 72 h ( $P < 0.05$ ). Compared with those at 0 h, both groups exhibited reduced RI and OI ( $P < 0.05$ ). Compared with group A, RI and OI were lower in group B at 24 h and 72 h ( $P < 0.05$ ). Serum levels of KL-6 and CC16 in group B after treatment were lower than those in group A ( $P < 0.05$ ). Conclusion: In contrast to SIMV, i-HFOV showed better efficacy in terms of blood gas indices, inflammation levels, the incidence of adverse reactions and safety in NRF.

**Keywords:** Synchronous intermittent mandatory ventilation, invasive high-frequency oscillatory ventilation, neonatal respiratory failure, KL-6, CC16

## Introduction

Respiratory failure is a type of pulmonary dysfunction caused by a variety of respiratory diseases, resulting in carbon dioxide retention or circulating hypoxia [1]. Neonatal respiratory failure (NRF) has a high incidence in the neonatal period and is the main cause of neonatal death [2]. The neonatal rib cage and lungs are immature, and low lung volumes easily increase airway resistance, which inhibits alveolar expansion and leads to ventilation-perfusion (V/Q) mismatching and eventually respiratory failure [3, 4]. There are many factors contribute to NRF, including neonatal asphyxia, wet lungs, and lung infections. It develops rapidly, and if

impaired lung function is not improved in time, adverse reactions will occur, which may even be life-threatening [5, 6].

Pulmonary gas exchange should be effectively optimized by mechanical ventilation in NRF to improve neonatal hypoxemia [7]. Modes of mechanical ventilation include synchronous intermittent mandatory ventilation (SIMV) and invasive high-frequency oscillatory ventilation (i-HFOV). In contrast to SIMV, i-HFOV is more conducive to promoting pulmonary gas exchange and improving respiratory failure in a short time. The patient's pulmonary compliance and carbon dioxide elimination are improved with increased oxygenation [8, 9]. Levels of

KL-6 and CC16 may serve as biomarkers for diagnosis and treatment of NRF. The expression of these two indices is obviously abnormal in pulmonary diseases. They are involved in pulmonary inflammation, reconstruction of lung tissue and the process of tumorigenesis and metastasis [10, 11].

Although clinical studies have confirmed that both SIMV and i-HFOV can improve symptoms in patients with chronic lung disease, their efficacy in NRF is still unclear [12, 13]. Therefore, this study mainly compared the application effects of SIMV and i-HFOV and explored its effect on KL-6 and CC16 levels in NRF.

### Materials and methods

#### Data

The clinical data of 113 neonates with respiratory failure were analyzed retrospectively and divided into group A (n = 56) and group B (n = 56) according to the ventilation modes. Group A received SIMV and group B received i-HFOV. (1) Inclusion criteria: neonates with symptoms including a respiratory rate of  $\geq 60$  breaths/min, central cyanosis, moaning, and three concave signs after birth; neonates who met the diagnostic criteria for NRF [14]; and neonates with  $\text{PaCO}_2 > 60$  mmHg were included. The study was approved by the Medical Ethics Committee of our Hospital. Written informed consent was obtained from the guardians of neonates. (2) Exclusion criteria: neonates with contraindications for treatment; congenital dysfunction; pulmonary artery occlusion and deformity; congenital diaphragmatic hernia; intrauterine infection; and myocarditis or cardiomyopathy were excluded.

#### Methods

Group A: Stephen Cordina neonate ventilator; SIMV mode; initial breathing frequency 20-50 times/min; tidal volume 6-8 ml/kg; ventilation volume 4-10 L/min, peak airway pressure 18-26 cm H<sub>2</sub>O; airway pressure <15 cm H<sub>2</sub>O, FiO<sub>2</sub> 25%-100%. The parameters were adjusted according to the actual conditions to effectively maintain the stability of blood gas, and provide nutritional support for the children when necessary to ensure stable state.

Group B: SLE5000 Infant ventilator; HFOV mode; initial frequency 9-15 Hz, oscillatory pressure 27-4015 cm H<sub>2</sub>O; airway pressure

8-16 cm H<sub>2</sub>O; FiO<sub>2</sub> 30%-100%. During ventilation, vital signs of children were monitored for parameter adjustments to stabilize blood gas. Nutritional support was provided for patients to maintain a stable state.

#### Observation outcomes

Criteria for curative effect. Effective: symptoms have been significantly improved or completely disappeared, and the oxygenation index has returned to normal or has been significantly improved; Ineffective: condition has not changed, or even further worsened [15].

Time on ventilators, oral feeding time and length of stay were compared between the two groups.

The incidence of adverse reactions such as lower respiratory tract infection, ventilator-associated pneumonia, and pulmonary hemorrhage during treatment were analyzed.

Blood gas indices such as PaO<sub>2</sub> and PaCO<sub>2</sub> were recorded at 0 h, 24 h, and 72 h, respectively. Respiratory index (RI) and oxygenation index (OI) were calculated [16].

Serum KL-6 and CC16 levels: 3 ml venous blood was taken from the two groups 1d before and after treatment, and centrifuged at 3000 r/min for 10 min to obtain the supernatant. Serum KL-6 and CC16 levels were measured using enzyme-linked immunosorbent assay and the operation was carried out in strict accordance with kit instructions (Shanghai Shengong Biological Engineering Co., Ltd.)

#### Statistical analysis

SPSS 22.0 was the analysis tool. Measurement data are expressed as mean  $\pm$  standard deviation (mean  $\pm$  SD). Data with normal distribution were subjected to *t* test, and data with non-normal distribution were subjected to Mann-Whitney U test; Enumeration data are expressed with [n (%)] and examined by chi-squared test. *P*<0.05 indicated statistical significance.

### Results

#### Comparison of baseline data

There was no difference in baseline data, including newborn gender, gestational age,

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**Table 1.** Comparison of baseline data [n (%)]/( $\bar{x} \pm s$ )

Data	Group A (n = 56)	Group B (n = 57)	t/ $\chi^2$	P
Gender (cases)				
Male	33 (58.93)	35 (61.40)	0.072	0.788
Female	23 (41.07)	22 (38.60)		
Gestational age (weeks)	36.85 $\pm$ 1.29	36.89 $\pm$ 1.33	0.162	0.871
Weight (kg)	1.78 $\pm$ 0.25	1.75 $\pm$ 0.23	0.664	0.508
Delivery options (Cases)				
Natural birth	40 (71.43)	39 (68.42)	0.122	0.727
Cesarean section	16 (28.57)	18 (31.58)		
Type of infants (Cases)				
Full term	37 (66.07)	35 (61.40)	0.266	0.606
Premature baby	19 (33.93)	22 (38.60)		

**Table 2.** Comparison of clinical efficacy between the two groups [n (%)]

Group	Number of cases	Effective	Ineffective
Group A	56	42 (75.00)	14 (25.00)
Group B	57	53 (92.98)*	4 (7.02)*
$\chi^2$		6.821	
P		0.009	

Note: \*indicates comparison with group A,  $P < 0.05$ .

**Table 3.** Comparison of clinical indicators between the two groups ( $\bar{x} \pm s$ )

Group	Time on ventilator (h)	Oral feeding time (h)	Length of stay (d)
Group A (n = 56)	95.63 $\pm$ 5.28	118.96 $\pm$ 6.86	16.52 $\pm$ 3.68
Group B (n = 57)	58.02 $\pm$ 2.39*	98.12 $\pm$ 2.28*	11.06 $\pm$ 1.28*
t	48.921	21.747	10.570
P	0.000	0.000	0.000

Note: \*indicates comparison with group A,  $P < 0.05$ .

weight, and childbirth delivery options between the two groups ( $P > 0.05$ ) (**Table 1**).

### Comparison of the effective rate

The effective rate of group B was 92.98%, which was higher than 75.00% in group A ( $P < 0.05$ ) (**Table 2**).

### Comparison of clinical indicators between two groups

The time on ventilator in group B was (58.02  $\pm$  2.39) h, which was shorter than (95.63  $\pm$  5.28) h in group A. The oral feeding time in group B

was (98.12  $\pm$  2.28) h, which was shorter than (118.96  $\pm$  6.86) h in group A. The length of hospital stay in group B was (11.06  $\pm$  1.28) d, which was shorter than (16.52  $\pm$  3.68) d in group A ( $P < 0.05$ ) (**Table 3**).

### Comparison of the incidence of adverse reactions

The incidence of adverse reactions was 7.02% in group B, which was lower than 21.43% in group A ( $P < 0.05$ ) (**Table 4**).

### Comparison of PaO<sub>2</sub> and PaCO<sub>2</sub> between the two groups

PaCO<sub>2</sub> at 0 h, 24 h, and 72 h were (65.21  $\pm$  2.56) mmHg, (49.98  $\pm$  9.62) mmHg, (42.52  $\pm$  5.18) mmHg respectively, in group A; and (65.28  $\pm$  2.16) mmHg, (42.12  $\pm$  2.18) mmHg, (36.12  $\pm$  1.09) mmHg respectively in group B. PaO<sub>2</sub> at 0 h, 24 h, 72 h were (43.25  $\pm$  8.12) mmHg, (61.02  $\pm$  5.18) mmHg, (75.12  $\pm$  2.36) mmHg respectively in group A, and (43.28  $\pm$  8.09) mmHg, (72.15  $\pm$  8.15) mmHg, (86.15  $\pm$  9.98) mmHg respectively in group B. There was no significant difference in PaCO<sub>2</sub> and PaO<sub>2</sub> at 0 h between the two groups ( $P > 0.05$ ). Compared with 0 h, PaCO<sub>2</sub> decreased and PaO<sub>2</sub> increased at 24 h and 72 h in the two groups ( $P < 0.05$ ).

Compared with group A, group B showed lower PaCO<sub>2</sub> and higher PaO<sub>2</sub> at 24 h and 72 h ( $P < 0.05$ ) (**Figure 1**).

### Comparison of RI and OI

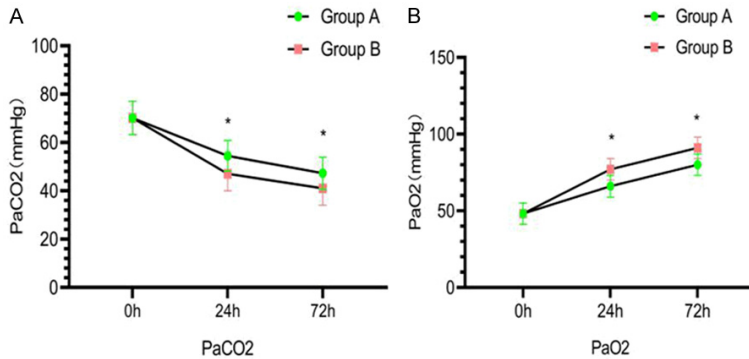
The RI at 0 h, 24 h and 72 h were respectively (2.62  $\pm$  0.15)%, (1.62  $\pm$  0.19)%, (0.99  $\pm$  0.13)% in group A; and (2.65  $\pm$  0.12)%, (1.19  $\pm$  0.11)%, (0.62  $\pm$  0.12)% respectively in group B. The OI at 0 h, 24 h, 72 h were respectively (8.62  $\pm$  0.16)%, (6.89  $\pm$  0.78)%, (5.88  $\pm$  0.62)% in group A; and (8.65  $\pm$  0.12)%, (5.62  $\pm$  0.12)%, (4.25  $\pm$  0.12)% respectively, in group B. There was no significant difference in RI and OI between the

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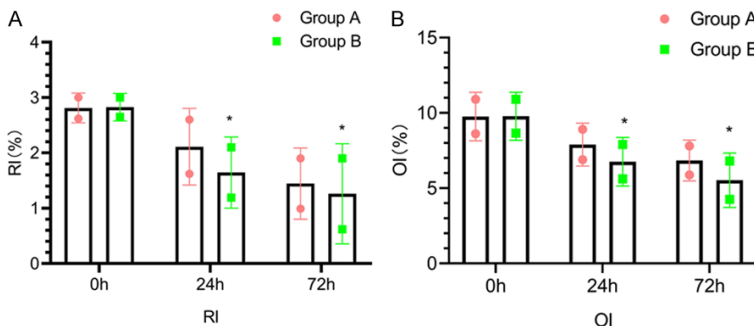
**Table 4.** Comparison of the incidence of adverse reactions between the two groups [n (%)]

Group	Number of cases	Lower respiratory tract infection	Ventilator-associated pneumonia	Pulmonary hemorrhage	Total
Group A	56	5 (8.93)	3 (5.36)	4 (7.14)	12 (21.43)
Group B	57	2 (3.51)	1 (1.75)	1 (1.75)	4 (7.02)*
$\chi^2$					4.827
<i>P</i>					0.028

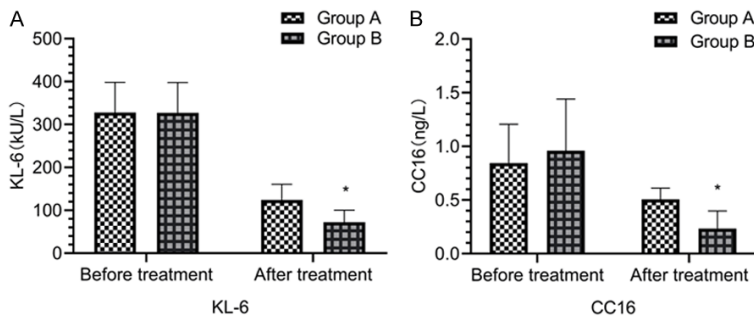
Note: \*indicates comparison with group A,  $P < 0.05$ .



**Figure 1.** Comparison of PaO<sub>2</sub> and PaCO<sub>2</sub>. Compared with group A, group B showed lower PaCO<sub>2</sub> and higher PaO<sub>2</sub> at 24 h and 72 h. \*Compared with group A,  $P < 0.05$ .



**Figure 2.** Comparison of RI and OI. In contrast with group A, group B had lower RI and OI at 24 h and 72 h. \*Compared with group A,  $P < 0.05$ .



**Figure 3.** Comparison of serum KL-6 and CC16 levels in two groups. The serum KL-6 and CC16 levels of group B were lower than those in group A. \*Compared with group A,  $P < 0.05$ .

two groups ( $P > 0.05$ ). In contrast to values at 0 h, the RI and OI of the two groups decreased at 24 h and 72 h ( $P < 0.05$ ). Compared with group A, RI and OI of group B were lower at 24 h and 72 h ( $P < 0.05$ ) (Figure 2).

### Comparison of serum KL-6 and CC16 levels

The levels of serum KL-6 and CC16 before treatment in group A were ( $277.58 \pm 12.26$ ) kU/L and ( $0.59 \pm 0.03$ ) ng/L, and those in group B were ( $277.62 \pm 12.21$ ) kU/L and ( $0.62 \pm 0.02$ ) ng/L, exhibiting no significant difference ( $P > 0.05$ ). After treatment, the serum KL-6 in group B was ( $52.12 \pm 9.12$ ) kU/L, lower than ( $98.22 \pm 10.08$ ) kU/L in group A, and the serum CC16 level was ( $0.12 \pm 0.02$ ) ng/L in group B, lower than ( $0.43 \pm 0.08$ ) ng/L in group A ( $P < 0.05$ ) (Figure 3).

### Discussion

Newborns have higher airway resistance compared with adults, and their inspiratory reserve volume is relatively low, which essentially affects the synthesis of pulmonary surfactant (PS), leading to fatigue of respiratory muscles and respiratory failure of neonates [17, 18]. Studies have shown that respiratory failure is an important cause of neonatal death, especially the

death of premature infants within 3 days of birth [19]. NRF is mainly manifested as dyspnea, accompanied by hypoxia symptoms such as cyanosis and purple skin, and severe airway obstruction, which impairs gas exchange and develops into three concave signs. Obstruction to airflow will lead to neonatal hypoxia, carbon dioxide retention, and metabolic disorders of organs, and significantly inhibit essential physiological functions [20, 21].

Currently, the main purpose of treatment for NRF is to reduce dyspnea as soon as possible and restore the systemic oxygen supply. Treatment options include noninvasive mechanical ventilation, invasive mechanical ventilation, pulmonary surfactant, nitrogen dioxide inhalation, extracorporeal membrane oxygenation (ECMO), etc., while pulmonary surfactant and mechanical ventilation have been widely accepted in China [22, 23]. Mechanical ventilation therapy works by blowing air or a mixture of gases (like oxygen and air) into the lungs at a set pressure for gas exchange, creating micro channels for gas flow, and improving hypoxic conditions. Neonatal respiratory system is not fully developed, especially premature infants, who are prone to apnea, so mechanical ventilation is the best treatment option. Most infants with respiratory failure will have pathological features such as pulmonary hyperinflation, alveolar edema, or alveolar atrophy. If proper mechanical ventilation is not selected, a series of serious complications such as pulmonary parenchymal damage and ventilator-associated infections may occur [24]. At the same time, it may also affect the blood supply to the brain and contribute to brain diseases, or hearing or visual impairments in infants.

This study compares the effects of SIMV and i-HFOV in the treatment of NRF. The results showed that the treatment efficiency of group B was higher than that of group A. The time on ventilator, oral feeding time and length of stay in group B were shorter than those in group A, and the blood gas indices in group B were better than those in group A after treatment ( $P < 0.05$ ), suggesting that the i-HFOV is better than SIMV with regard to improvements in blood gas indices. The reason may be that ventilation frequency of i-HFOV is four times

higher than SIMV, and its tidal volume is lower, promoting gas exchange. Secondly, this ventilation mode generates biphasic positive airway pressure through small periodic pressure variations and high-frequency oscillations, which makes the alveoli expand in a short period of time without increasing the incidence of barotrauma, and promotes lung compliance and oxygen infusion and carbon dioxide release [25]. Compared with SIMV, i-HFOV can effectively prevent lung injury caused by mechanical ventilation and improve the neonatal survival rate [26].

CC16 could effectively antagonize exogenous foreign body protein and has a significant anti-inflammatory effect. KL-6, an inflammatory mediator, is commonly expressed in type II alveolar epithelial cells and has a strong chemotactic effect on myofibroblasts [27]. Serum CC16 and KL-6 levels in the damaged lung tissues were significantly increased and positively correlated with the severity of the disease. Children with respiratory failure are affected by symptoms such as hypoxia and acidosis, which can obviously damage pulmonary vascular endothelial cells and alveolar epithelial cells, cause pulmonary alveolar and pulmonary interstitial edema, improve pulmonary capillary permeability, and damage type II alveolar epithelial cells. Apoptosis of type II alveolar epithelial cells will lower the physiological activity of lung surfactant, reduce oxygenation levels, and damage lung function [28, 29]. The results of this study showed that serum levels of KL-6 and CC16 in group B after treatment were lower than those in group A ( $P < 0.05$ ), suggesting that the i-HFOV improves inflammation levels better than SIMV, which may be due to the fact that i-HFOV increases the alveolar ventilation, reduces the airway resistance, and promotes the ciliary movement of the respiratory tract and the discharge of inflammatory foreign bodies in the lungs through the resonance effect. This study also showed that the incidence of adverse reactions in group B was lower than that in group A. This may be because i-HFOV increases the arterial partial pressure of oxygen and optimizes alveolar expansion state, which significantly reduces the risk factors during tracheal intubation and reduces the incidence of adverse reactions.



In summary, compared with SIMV, i-HFOV shows superior treatment efficacy with regard to the improvement of blood gas indices, inflammation status and adverse reactions in NRF.

Although this study has achieved certain results, there are the limitations of a small sample size, and studies with larger sample size and longer follow-up will be conducted in the future.

### Disclosure of conflict of interest

None.

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