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Original article

High-frequency oscillatory ventilation in children with acute respiratory distress syndrome: experience of a pediatric intensive care unit☆

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A B S T R A C T

Objective: To describe the effects of high-frequency oscillatory ventilation (HFOV) as a rescue ventilatory support in pediatric patients with acute respiratory distress syndrome (ARDS).

Methods: Twenty-five children (1 month < age < 17 years) admitted to a university hospital pediatric intensive care unit (ICU) with ARDS and submitted to HFOV for a minimum of 48 hours after failure of conventional mechanical ventilation were assessed.

Results: 28 days after the onset of ARDS, the mortality rate was 52% (13/25). Over the course of 48 hours, the use of HFOV reduced the oxygenation index [38 (31-50) vs. 17 (10 - 27)] and increased the ratio of partial arterial pressure O_2 and fraction of inspired O_2 [65 [44-80) vs. 152 (106-213)]. Arterial CO_2 partial pressure [54 (45-74) vs. 48 (39-58) mmHg] remained unchanged. The mean airway pressure ranged between 23 and 29 cmH_2O. HFOV did not compromise hemodynamics, and a reduction in heart rate was observed (141 ± 32 vs. 119 ± 22 beats/min), whereas mean arterial pressure (66 ± 20 vs. 71 ± 17 mmHg) and inotropic score [44 (17-130) vs. 20 (16-75)] remained stable during this period. No survivors were dependent on oxygen.

Conclusion: HFOV improves oxygenation in pediatric patients with ARDS and severe hypoxemia refractory to conventional ventilatory support.

☆Study conducted at Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

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Ventilação oscilatória de alta frequência em crianças com síndrome da angústia respiratória aguda: experiência de um centro de tratamento intensivo pediátrico

Palavras-chave:
Síndrome da angústia respiratória aguda
Ventilação de alta frequência oscilatória
Insuficiência respiratória
Pediatria
Ventilação mecânica protetora

R E S U M O

Objetivo: Descrever os efeitos da aplicação da ventilação de alta frequência oscilatória como suporte ventilatório de resgate em uma série de pacientes pediátricos com síndrome da angústia respiratória aguda (SARA).

Métodos: Participaram do estudo 25 crianças (> 1 mês e < 17 anos) internadas em uma UTI pediátrica universitária com SARA e submetidas à ventilação de alta frequência oscilatória (VAFO) por um mínimo de 48 horas, após falha da ventilação mecânica convencional.

Resultados: A taxa de mortalidade foi de 52% (13/25) 28 dias após o início da SARA. Ao longo de 48 horas, a aplicação da VAFO reduziu o índice de oxigenação [38 (31-50) vs. 17 (10-27)] e aumentou a relação pressão arterial parcial de O_2/fração inspirada de O_2 [65 (44-80) vs. 152 (106-213)]. A pressão arterial parcial de CO_2 [54 (45-74) vs. 48 (39-58) mmHg] manteve-se inalterada. A pressão média de vias aéreas oscilou entre 23 e 29 cmH_2O. A VAFO não comprometeu a hemodinâmica e observou-se uma redução da frequência cardíaca (141 ± 32 vs. 119 ± 22 bat/min), a pressão arterial média (66 ± 20 vs. 71 ± 17 mmHg) e o escore inotrópico [44 (17-130) vs. 20 (16-75)] mantiveram-se estáveis nesse período. Nenhum sobrevivente ficou dependente de oxigênio.

Conclusão: VAFO melhora a oxigenação de pacientes pediátricos com SARA grave e hipoxemia refratária ao suporte ventilatório convencional.

Introduction

The prevalence of acute respiratory distress syndrome (ARDS) in pediatric intensive care units varies from 2% to 7.6%.[1,2] In pediatrics, ARDS is associated with high mortality rates, which vary according to the service, population studied, and risk factors. Clinical studies suggest that mechanical ventilation (MV) may modify inflammatory responses in patients with acute lung injury. In patients with prior pulmonary and systemic inflammation, ventilation with tidal volumes (V_T) of 10-15 mL/kg of ideal body weight (IBW) and moderate-to-low levels of positive end-expiratory pressure (PEEP) are associated with increased levels of intra-alveolar and systemic inflammatory mediators.[3] In contrast, mechanical ventilation with moderate-to-high levels of PEEP and reduced V_T of approximately 6 mL/kg of IBW ensured proper gas exchange, reduced systemic and intra-alveolar inflammatory mediators, and decreased mortality.[3-6]

The use of protective ventilatory strategies that prevent further lung injury associated with MV is a major concern in any patient, including those without acute pathology.[7] High-frequency oscillatory ventilation (HFOV) is a protective ventilatory strategy, as it optimizes alveolar recruitment and lung volume, as well as improves oxygenation by applying high-flow rates and frequencies up to 900 cycles per minute with reduced tidal volumes (1-2 mL/kg) resulting from minor differences in inspiratory and expiratory pressures, producing a high and persistent mean airway pressure.[8]

HFOV appears to represent an important therapeutic option in ventilatory support of children with respiratory failure. Despite the increased use of HFOV in pediatric patients with acute respiratory failure, there have been few published studies, as well as few prospective studies and randomized clinical trials involving children with ARDS.[9-12] HFOV has been more often used as a rescue therapy in children with severe respiratory failure after failure of conventional mechanical ventilation (CMV) with lung protective strategies.[12-15] However, to date there is insufficient evidence to support its use.[16,17] When HFOV is shown to be effective as a rescue therapy, this ventilation mode will become an extremely useful therapeutic option.[18,19]

The present study aimed to describe the effects of the use of HFOV as a rescue ventilatory support over oxygenation and ventilation in pediatric patients diagnosed with ARDS.

Methods

Study design

This was an observational and retrospective study performed through the analysis of medical records of children admitted between 2005 and 2010 with ARDS,[20] submitted to HFOV due to treatment failure with conventional mechanical ventilation.

Patient selection

The study was performed at the pediatric ICU of the Hospital da Criança Santo Antônio, which has 30 beds in a university hospital complex. The study was approved by the Ethics

Committee of the Complexo Hospitalar Santa Casa de Porto Alegre (registration No.: 1935/08).

Patients were considered eligible for the study according to the following criteria: a) 1 month < age < 17 years, b) used HFOV for ARDS management (chest X-ray with bilateral infiltrates, ratio of partial pressure of arterial oxygen and inspired oxygen fraction [PaO_2/FiO_2] ≤ 200, and no clinical evidence of left atrial hypertension); c) failed protective conventional mechanical ventilation (CMV) (children: peak inspiratory pressure [PIP] > 35 cmH_2O, mean airway pressure [MAwP] > 15-18 cmH_2O and $FiO_2 \geq 0.6$; term infants: MAwP ≥ 10-12 cm H_2O, $FiO_2 \geq 0.6$, and failure to increase lung volume); and d) complete medical records. The decision to switch to HFOV considering the difficulty to maintain ventilatory parameters/oxygenation was made by the attending physician.

Patients were excluded from the study if HFOV was applied for less than 48 hours in the event of death or early weaning from HFOV in the same period.

Data were collected on diagnosis (primary and associated) and outcome variables (time in HFOV, time in CMV before and after HFOV, duration of ICU stay, in-hospital mortality, and mortality at day 28 after the ARDS diagnosis).

Ventilatory strategies

Conventional mechanical ventilation

Initially, all patients used pressure-controlled CMV (Servo 300, Siemens-Elema AB –Sweden; SERVOi, Maquet GmbH & Co, KG – Rastatt, Germany). The ventilation strategy consisted of "protective ventilation" with $FiO_2 < 0.5$, tolerating a saturation of arterial hemoglobin oxygen (SaO_2) > 85%, permissive hypercapnia as long as pH > 7.2, and a tidal volume < 7 mL/kg of ideal body weight. The ventilation mode used was synchronized intermittent mandatory ventilation with controlled pressure and assisted pressure. The general support included sedation (continuous infusion of opioid and benzodiazepine), fluid maintenance, nutritional support, and antibiotics when indicated. Whenever necessary, a muscle relaxant (pancuronium) was used to facilitate mechanical ventilation. Hemodynamic support with vasopressors/inotropes and/or fluids was administered through a central venous catheter when necessary.

High-frequency oscillatory ventilation

All patients submitted to HFOV were ventilated with a High-Frequency Oscillator Sensor Medics 3100B (Sensor Medics – Yorba Linda, CA, USA). Until the year 2007, there was no protocol for the start of HFOV, and HFOV parameters were chosen at the discretion of the attending physician. From 2008 onward, the following protocol was adopted: MAwP = 5 cmH_2O above the MAwP in CMV, FiO_2 = 1.0, amplitude adjusted to achieve adequate power for chest wall vibration, and airflow maintained at 30 mL/min. The initial oscillatory frequency was adjusted between 10-15 Hz. To attain HFOV weaning, FiO_2 was kept between 0.4 and 0.6, followed by a decrease of 1 to 2 cmH_2O to decrease airway pressure. Regarding ventilation, there were progressive reductions (3-5 cmH2O) in amplitude pressure. CMV would be resumed when airway pressure was ≤ 20 cmH_2O, $FiO_2 \leq 0.4$, and when the patient tolerated the aspiration of the endotracheal tube without oxygen saturation decrease.[21,22]

Monitoring

Arterial blood gases and ventilatory parameters were collected in CMV (peak inspiratory pressure [PIP], positive pressure at the end of exhalation, positive end-expiratory pressure [PEEP], respiratory rate [RR], fraction of inspired oxygen [FiO_2], inspiratory time) at the beginning of HFOV use and after 6, 12, 24, and 48 hours (mean airway pressure [MAwP], amplitude [AMP], RR, FIO_2). The oxygenation index (OI = [MAwP X FIO_2 X 100]/PaO_2)[23] and the PaO_2/FiO_2 ratio were calculated in the same time intervals. Hemodynamic parameters (heart rate [HR] and mean arterial pressure [MAP]) and inotropic score (dopamine X 10 + adrenaline X 100) were obtained over 48 hours.[24] Patient severity was evaluated through the Pediatric Index of Mortality (PIM) score.[25]

Statistical analysis

Analysis of variance and Student's *t*-test were used to analyze the data with normal distribution (Tukey's test for comparisons). The nonparametric Mann-Whitney test and Friedman's ANOVA (Dunn test for comparisons) were used for variables with non-normal distribution. Results were expressed as mean ± standard deviation or median (25-75 percentile).

Results

Patient characteristics

Table 1 describes patient characteristics and mortality rates. There were 31 identified patients who were diagnosed with ARDS, submitted to HFOV during a five-year period. Six patients were excluded; five died within less than 24 hours, and one was weaned from HFOV before 48 hours, leaving 25 patients at the final analysis. The patients had high risk of death with high mortality rate and aggressive ventilatory support before the use of HFOV. The associated comorbidities were: postoperative of congenital surgery (n = 6), Cushing's syndrome (n = 1), anoxic encephalopathy (n = 3), hematologic malignancies (n = 3), major burn injury (n = 1), late complications of kidney transplantation (n = 1), cytomegalovirus (n = 1), pulmonary lymphangioma (n = 1), postoperative of late kidney transplantation (n = 1), prematurity (n = 3), neonatal anoxia (n = 1), hyaline membrane disease (n = 1), bronchopulmonary dysplasia (n = 1), postoperative of pulmonary surgery (n = 2), and nonspecific immune deficiency (n = 1).

Ventilation and oxygenation parameters

After 48 hours of HFOV, FiO_2 decrease and a significant increase in SaO2 were achieved. The effect of HFOV on patients' significant ventilatory improvement was verified by reducing

Table 1 – Patient characteristics, respiratory failure severity, and clinical outcomes.

Variables	n = 25
Age (months)	9 (4-81)
Weight (kg)	7 (4-19)
Gender (M/F)	13/12
PIM	30 ± 24
Mortality rate 28 days after ARDS	52% (13/25)
Time in ICU (days)	19 (13-37)
Time of HFOV (h)	82 (72-144)
Time in ICU pre-death (days)	17 (12-37)
Time of CMV pre-HFOV (hours)	24 (19-144)
Time of CMV post-HFOV (hours)	72 (0-276)
PIP (mmHg)	37 ± 6
PEEP (cmH_2O)	11 ± 4
RR (resp/min)	34 ± 9
FiO_2	0.95 ± 0.13
Diagnosis	
Pneumonia	9
Pneumonia (RSV+)	1
Bronchiolitis (RSV+)	5
Bronchiolitis	2
Extra-pulmonary ARDS	6

ARDS, acute respiratory distress syndrome; CMV, conventional mechanical ventilation; F, female; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; HFOV, high-frequency oscillatory ventilation; M, male; PEEP, positive end-expiratory pressure; PIM, pediatric index of mortality; PIP, peak inspiratory pressure; RR, respiratory rate; RSV, respiratory syncytial virus.
Data are shown as median (25-75 percentiles) or mean ± standard deviation.
Each patient may have had more than one diagnosis.

the oxygenation index and increasing the PaO_2/FiO_2 ratio (Fig. 1) over 48 hours. $PaCO_2$ remained almost unchanged. The MAwP necessary to maintain oxygenation with progressive reduction of FiO_2 during the 48 hours of HFOV ranged between 23 and 29 cmH_2O.

Hemodynamic parameters

Before HFOV use, 20 patients were receiving one or a combination of vasoactive drugs; 24 hours after the start of HFOV, three other patients needed a drug or combination of vasoactive drugs (dopamine, n = 22; noradrenaline, n = 6; adrenaline, n = 10; milrinone, n = 3). The two main causes of hemodynamic instability were septic shock (n = 17) and postoperative of heart surgery. Only two patients did not need vasoactive drugs. Even with high mean airway pressures, hemodynamic performance was not impaired by HFOV; it was also observed that HR decreased significantly and MAP remained stable. Moreover, the inotropic score remained unchanged during the evaluation period.

In seven patients with bronchiolitis, the PaO_2/FiO_2 ratio increased from 62 ± 25 to 193 ± 114 (p = 0.027), and OI decreased from 48 ± 17 to 15 ± 7 (p = 0.001) over 48 hours. Furthermore, the $PaCO_2$ decreased (59 ± 17 vs. 42 ± 10 mmHg, p = NS) during this same period.

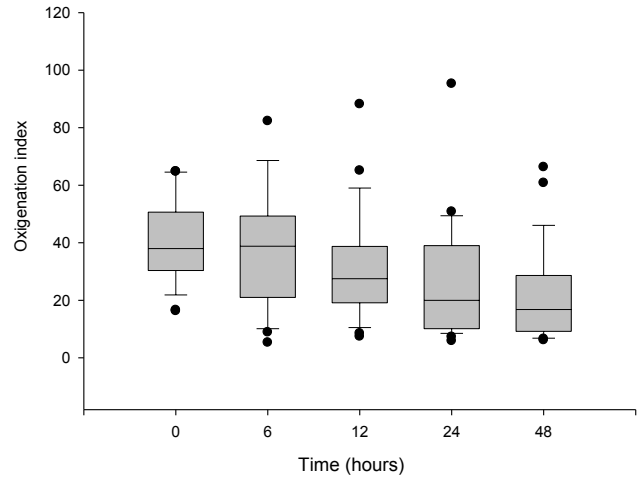

Figure 1 – Changes in oxygenation index and arterial partial pressure of oxygen/fraction of inspired oxygen during the initial 48 hours of high-frequency oscillatory ventilation (HFOV). HFOV was established at time 0, which represents the values immediately before the HFOV. Values are expressed as median with 25-75% percentiles. [a]p < 0.001 (Friedman's ANOVA); [b]p < 0.05, compared to the previous level (Tukey's test).

Clinical outcomes

Table 1 shows the main clinical outcomes. The improvement of the parameters related to oxygenation was higher in survivors than in non-survivors (Table 2). No survivors were dependent on oxygen. Among the complications potentially related to ventilation and/or pulmonary disease, ten patients had nonhypertensive pneumothorax without additional hemodynamic involvement.

Comparison between the pre-protocol and post-protocol periods of high-frequency oscillatory ventilation implementation

Table 3 describes the comparison of the main physiological and clinical outcomes for the two periods. No significant differences were observed among the seven patients who were ventilated without an adjuvant protocol and the remaining 18 patients who were ventilated based on the established HFOV protocol since 2008.

Discussion

The present study, which involved a sample of patients with severe ARDS submitted to rescue HFOV, did not allow for the determination of the true effectiveness of this method. However, the results indicate that HFOV significantly improves gas exchange and allows reductions in oxygen supply. These findings are consistent with other studies that evaluated the use of HFOV in pediatric patients with ARDS, and suggest that the benefit would be greater with an earlier start of

Table 2 – Alterations in blood gas, oxygenation, and hemodynamic variables within the first 48 hours.

Variables[a]	0 h	6 h	12 h	24 h	48 h	p value[b]
PaO_2, mmHg	64 (46-77)	70 (55-98)	75 (61-96)	73 (48-98)	74 (56-96)	0.749
FiO_2	0.95 ± 0.13	–	–	–	0.55 ± 0.22	< 0.001
$SatO_2$, %	86±10	86 ± 20	93 ± 8*	92 ± 11	91 ± 13	0.001
$PaCO_2$, mmHg	54 (45-74)	54 (36-72)	52 (39-65)	40 (34-58)	48 (39-58)	0.620
MAwP, cmH_2O	23.7 ± 3.4	29.2 ± 4.0[b]	29.0 ± 3.8	27 ± 4.5	25.5 ± 5.5	< 0.001
HR, beats/min	141 ± 32	140 ± 15	133 ± 20	126 ± 20	119 ± 22*	0.002
Temp, ºC	36.4 ± 1.4	36.2 ± 0.8	36.2 ± 0.7	36.0 ± 0.9	35.6 ± 0.9	0.068
MAP, mmHg	66 ± 20	65 ± 16	72 ± 19	72 ± 15	71 ± 17	0.149
Inotropic score	44 (17-30)	45 (30-110)	35 (16-58)	22 (15-74)	20 (16-75)	0.243

FiO_2, fraction of inspired oxygen; HR, heart rate; MAP, mean arterial pressure; MAwP, mean airway pressure; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide, $SatO_2$, arterial oxygen saturation; Temp, temperature.
[a]Described by median (percentiles 25-75) or mean ± SD. Analysis of variance (ANOVA) or Friedman's test.
[b]$p < 0.05$ comparatively to the previous level (Tukey's or Dunn's test).

Table 3 – Changes in blood gas and oxygenation variables within the first 48 hours for non-survivors (NS, n = 13) and survivors (S, n = 12) after 28 days of acute respiratory distress syndrome.

Variables[a]		0 h	6 h	12 h	24 h	48 h
PaO_2, mmHg	NS	56 (46-73)	67 (42-86)	66 (48-79)	65 (43-90)	59 (52-76)
	S	65 (47-77)	74 (61-115)	92 (77-109)	78 (62-108)	88 (71-118)
PaO_2/FiO_2	NS	56 (42-73)	69 (56-138)	109 (75-151)[b]	123 (75-145)	112 (82-139)
	S	67 (47-88)	94 (73-171)	116 (92-175)	145 (123-271)[b]	197 (161-267)[a]
OI	NS	41 (36-59)	39 (24-59)	27 (22-46)	22 (13-42)	17 (14-35)
	S	35 (27-44)	34 (13-42)	28 (13-33)	19 (10-25)	13 (7-21)
$PaCO_2$, mmHg	NS	48 (43-63)	55 (38-67)	44 (36-66)	39 (34-51)	47 (44-52)
	S	63 (48-76)	54 (31-76)	59 (42-69)	45 (34-68)	44 (37-52)

FiO_2, fraction of inspired oxygen; OI, oxygenation index; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.
[a]$p < 0.005$ comparatively to the previous level (Dunn's test).
[b]$p = 0.004$ between groups.

HFOV, especially in the first 24 hours in cases associated with refractory hypoxemia.[10,16,26] Even though the median time of CMV before HFOV was around 24 hours in this study, it must be concluded that the indication was delayed. It can be observed that at the moment of transition, a mean FiO_2 of 95% was used in CMV, as well as a mean PIP of 37 mmHg, thus maintaining a high shunt fraction (refractory hypoxemia). Therefore, the use of HFOV should not be based on time of evolution, but on refractoriness to CMV.

The decision to indicate HFOV defined by a criterion of refractory response to CMV is reinforced by another observation from the present study. There were no differences between patients submitted to HFOV with no defined protocol (up to 2007) when compared with those in whom HFOV was used according to clear definitions of utilization. Patients did not differ in severity or ventilatory parameters at the beginning of HFOV implementation, and had the same clinical outcome. It can be speculated that the definition of decision criteria for changing the ventilatory method is more important than HFOV implementation using a strict protocol.

HFOV, even when started late, promoted significant improvement in OI and PaO_2/FiO_2 ratio during the 48 hours. Most studies have indicated HFOV as a rescue ventilatory support for ARDS patients who had difficulties in CMV with worsening of OI.[10,12,17] A survey among 14 centers, which included 232 pediatric patients, demonstrated a mean OI of 27 before HFOV.[12] In the present study, when HFOV was indicated, the mean OI was almost 40, confirming that the decision to perform the transition was probably late for most cases. Several studies have focused on OI as a predictor of mortality after the transition to HFOV.[12,16] Sarnaik et al. suggested that, in patients with initial OI < 20, the absence of a decrease of at least 20% in OI within the first six hours of HFOV may be considered a predictor of death.[15]

Classically, HFOV uses relatively high MAwP, allowing for a more effective maintenance of lung recruitment than that promoted by the use of PEEP in CMV.[22,27] In the present study MAwP increased significantly after start of HFOV, with significant improvement in oxygenation indices, suggesting the opening of a major portion of alveolar units with improved gas exchange (alveolar recruitment). The impact on $PaCO_2$ was not significant due to adjustments in the amplitude of the respirator, in order to prevent unnecessary and unwanted alveolar hyperventilation.[9,16,17,28]

With the increase in MAwP during HFOV, hemodynamic impairment can occur, as pleural pressure elevation

causes a decrease in venous return and cardiac output. Most patients in the present study were already receiving inotropic-vasoactive drugs during CMV; the use of HFOV did not impair hemodynamic stability and there was a decrease in hemodynamic support throughout the 48 hours. A study by Mehta et al. in adult patients showed that HFOV can lead to increased filling pressures and significant decrease in cardiac output.[29] In contrast, Derdak et al. found no significant differences in heart rate, mean arterial pressure, or cardiac output between adult patients undergoing HFOV *versus* those submitted to CMV within the first 72 hours of treatment.[30] Although cardiac output was not measured in the present study, the observed hemodynamic performance suggests that there was no additional blood flow impairment in the present patients, as MAP remained stable and HR decreased.

The mortality from ARDS in children has been decreasing to around 20%.[31-33] Although some researchers have estimated that it is higher,[34] with explicit protocols in certain populations of children with ARDS, mortality can be as low as 8%.[35] However, ARDS patients continue to be among those at higher risk in pediatric ICUs, with prolonged mechanical ventilation time and increased risk for nosocomial infections, as well as increased risk for unknown respiratory morbidities and neurodevelopmental injuries. In the present study, a mortality rate of 52% after 28 days of ARDS diagnosis and treatment with HFOV was observed. When evaluating the high mortality rate from ARDS observed in this group, it should be noted that: a) this was a selected group of patients with refractory hypoxemia in CMV (mean PIP of 30 and FIO_2 = 95%), b) a large number of patients presented septic shock and several co-morbidities, c) there was sample selection, which excluded from the study those patients in whom HFOV was used for less than 48 hours (milder cases), and d) there was a lack of an explicit protocol for conventional ventilatory support and transition to HFOV. It is known that the initial severity of the oxygenation defect, non-pulmonary organ failure, and the presence of neurological dysfunction are independent predictors of mortality in children with ARDS.[31] In studies of populations with similar severity, severe sepsis and multiple-organ failure are common causes of death in patients with ARDS, with a mortality rate that can reach 61%.[36]

The rate of pneumothorax after HFOV initiation was particularly high. However, no patient developed chronic lung disease, and no survivors remained more than 28 days on oxygen therapy. In the study by Arnold et al., the incidence of barotrauma was lower (25%), but the need for prolonged supplemental oxygen was of 21%.[10]

One of the contraindications related to HFOV is in patients with increased airway resistance, such as asthma and bronchiolitis.[21] Seven patients with bronchiolitis were ventilated through HFOV, of which three survived. Oxygenation improved significantly in these patients and there was a trend toward improved ventilation. The present results are similar to those obtained by Berner et al., who also demonstrated lower oxygen supplementation and improvement of other gas exchange parameters.[37] However, at the time of HFOV implementation, as the patients met the criteria for ARDS, it is possible that the benefit may have been observed on alveolar-interstitial alterations, characteristic of ARDS, and not on small airway obstruction, characteristic of bronchiolitis.

This study has certain limitations related to its retrospective design, the data from medical records that were sometimes incomplete, and the size and heterogeneity of the studied population sample. In addition, the study was performed in a single center; these limitations, when considered together, make any extrapolation of results uncertain.

Conclusion

In patients with severe ARDS and severe hypoxemia refractory to conventional ventilatory support, HFOV promotes sustained improvement in oxygenation indices.

However, randomized controlled trials are still needed to identify whether HFOV can become an alternative ventilatory method to conventional ventilation modes, and to establish the optimal time for its use.

Conflicts of interest

The authors declare no conflicts of interest.

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