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High-frequency oscillatory ventilation in paediatric patients with acute respiratory distress syndrome—early rescue use

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Abstract In order to determine the response to high-frequency oscillatory ventilation (HFOV), used as an “early rescue” therapy, in a cohort of paediatric patients with acute respiratory distress syndrome (ARDS), a prospective clinical study was performed in a tertiary care paediatric intensive care unit. Ten consecutive patients, aged 12 days to 5 years with ARDS and hypoxaemic respiratory failure on conventional ventilation (CV), using a lung protective strategy, were managed with HFOV early in the course of the disease process (median length of CV 4 h). Arterial blood gases, oxygenation index (OI), alveolar-arterial oxygen difference ($P(A-a)O_2$) and PaO_2/FIO_2 ratio were prospectively recorded prior to HFOV (0 h) and at predetermined intervals throughout the course of the HFOV protocol. There was a significant improvement in $PaCO_2$ 4 h after institution of HFOV ($P = 0.012$). A significant and sustained increase ($P < 0.001$) in PaO_2/FIO_2 ratio and a significant and sustained decrease ($P < 0.001$) in OI and $P(A-a)O_2$ were demonstrated during the HFOV trial. These improvements were achieved 4 h after initiating HFOV ($P < 0.05$). Eight patients survived. There were no deaths from respiratory failure. **Conclusion:** In paediatric patients with acute respiratory distress syndrome and hypoxaemic respiratory failure on conventional ventilation, using a lung protective strategy, high-frequency oscillatory ventilation used as an “early rescue” therapy, improves gas exchange in a rapid and sustained

fashion and provides a good outcome. Use of this therapy should probably be considered early in the course of the disease process.

Keywords Adult respiratory distress syndrome · High-frequency ventilation · Mechanical ventilation · Paediatrics · Respiratory insufficiency

Abbreviations ARDS: acute respiratory distress syndrome · CV: conventional ventilation · HFOV: high-frequency oscillatory ventilation · MAP: mean airway pressure · OI: oxygenation index · $P(A-a)O_2$: alveolar-arterial oxygen difference · PEEP: positive end-expiratory pressure · PIP: peak inspiratory pressure

Introduction

There is increasing appreciation that lung-protective strategies using small tidal volumes and high positive end-expiratory pressure (PEEP) levels are beneficial in patients with acute respiratory distress syndrome (ARDS) [15]. High-frequency oscillatory ventilation (HFOV), combining minimal pressure changes with a high continuous distending pressure, provides a theoretically attractive alternative to conventional lung-protective ventilatory modes.

HFOV has been reported to improve oxygenation in children with acute hypoxaemic respiratory failure and its role in the rescue of paediatric patients failing conventional ventilation (CV) is now relatively well established [1]. Because HFOV is considered to be a “rescue” therapy, intervention with HFOV is usually in the later stages of acute respiratory failure and the optimum timing of HFOV initiation, remains unclear.

The objective of this study was to report the outcome of a consecutive cohort of paediatric patients with ARDS treated with HFOV early in the course of the disease process.

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Subjects and methods

In the paediatric intensive care unit of the Children's Hospital of Tunis (Tunisia), we conducted, over a 2-year period, a prospective cohort study of ten consecutive paediatric patients with ARDS and relative hypoxaemic respiratory failure on CV, who were treated with HFOV used as "early rescue" therapy.

ARDS was defined as an acute onset of respiratory failure with bilateral diffuse infiltrates on a chest radiograph, a PaO₂/FIO₂ ratio <200 mm Hg and no clinical and echocardiographic evidence of left atrial hypertension. There were seven female and three male patients ranging in age from 12 days to 5 years (median 3.8 months). Five patients had pneumonia as the triggering aetiology of the ARDS (one due to respiratory syncytial virus, one due to parainfluenza virus, two due to *Mycoplasma pneumoniae* and one due to *Pneumocystis carinii*). The cause of ARDS in two patients was severe sepsis. One of them, who presented with prolonged high fever, erythema, gastroenteritis, occlusive syndrome, diffuse alveolar disease and shock, had systemic *Yersinia enterocolitica* infection. The second patient had, initially, bronchiolitis with localised alveolar disease. She developed ARDS, septic shock and multiple organ failure 40 h after admission and *Pseudomonas aeruginosa* was detected in blood cultures. In the three other patients, the cause of ARDS was indeterminate but history, clinical and radiological findings suggested lower airway infection. No microorganisms were detected in tracheal or blood samples in these patients who had no other organ failure. Moreover, the patient, who had *Pneumocystis carinii* pneumonia had immunodepression. Patient characteristics are given in Table 1. All patients had severe ARDS, as noted by a median Lung Injury Score [11] of 3.3 (range 2.3–4). The median Pediatric Risk of Mortality Score (PRISM) [12] was 18 (range 13–29) on admission with a risk of mortality equal to 25.8%.

Ventilation strategies

All patients were treated with CV, using either volume or pressure-controlled ventilation (Servo 900C and Servo 300, Siemens Medical Systems, Solna, Sweden), before institution of HFOV. We employed a strategy that utilised increases in PEEP and inspiratory time to increase mean airway pressure (MAP) and to limit increases in peak inspiratory pressure (PIP) at 30 cm H₂O. Tidal volume was kept below 7 ml/kg. Hypercarbia was tolerated if the arterial pH was above 7.25. All patients were sedated with a combination of opioid and benzodiazepine and immobilised with vecuronium. The median length of CV was 4 h (range 1–46 h). Only the patient with *Pseudomonas aeruginosa* septicaemia, who developed secondary ARDS, was ventilated for more than 24 h with CV, initially instituted for bronchiolitis (patient 6).

Table 1 Patient characteristics and severity of respiratory failure. Medians given in parentheses. (D died, MP *Mycoplasma pneumoniae*, PA *Pseudomonas aeruginosa*, PC *Pneumocystis carinii*, PIV parainfluenza virus, RSV respiratory syncytial virus, S survived, YE *Yersinia enterocolitica*)

Patient	Sex	Age	Diagnosis	Air leak	CV prior to HFOV (h)	MAP (cm H ₂ O) 0 h ^a	PIP (cm H ₂ O) 0 h ^a	OI (0 h) ^a	P (A-a)O ₂ (mmHg) 0 h ^a	PaO ₂ /FIO ₂ (mmHg) 0 h ^a	HFOV (h)	Outcome
1	M	12 days	RSV pneumonia	-	2.5	11.5	25	39	609	41.1	163	S
2	M	4 months	PIV pneumonia	+	1	13	25	21	525.6	67	140	S
3	F	49 days	MP pneumonia	-	20	15	28	28.5	611	54.7	384	S
4	F	5 years	MP pneumonia	-	4	18	34	28.5	635	56.2	133	S
5	F	8 months	PC pneumonia	-	4	10	20	9	380.1	100	180	S
6	F	50 days	Sepsis (PA)	-	46	17	25	29.2	596.2	53.3	24	D
7	M	5 years	Sepsis (YE)	-	4	16.5	35	33	618	48	133	D
8	F	7.5 months	Indeterminate	-	11	19	32	19.5	466	71.7	111	S
9	F	3.5 months	Indeterminate	+	3	13	25	17.2	412.2	70.9	88	S
10	F	2.5 months	Indeterminate	+	4 (4)	18 (15.8)	27 (26)	17.9 (2.5)	458.7 (561)	50.4 (55.5)	102 (6)	S

^aJust before initiation of HFOV (0 h)

HFOV was initiated because the FIO_2 requirements of the patients exceeded 0.6 to maintain an arterial oxygen saturation of $>90\%$. Three patients had a severe pulmonary air leak prior to instituting HFOV.

The high-frequency ventilator used was a piston-driven device that offers an active expiratory phase and a variable inspiration/expiration ratio (3100A, Sensor Medics, Yorba Linda, CA). We employed a "high-volume" strategy that consisted of incremental increases in MAP until arterial oxygen saturation was $>90\%$, with an FIO_2 of <0.6 and with avoidance of lung overdistension. Lung overdistension was identified using regular chest radiography and was defined as the presence of more than nine posterior ribs of lung expansion. Pressure amplitude of oscillation was initially adjusted to provide adequate chest wall movement and was subsequently titrated to maintain the $PaCO_2$ between 35 and 50 mm Hg. Initial frequency was set between 7 and 12 Hz. If adequate ventilation could not be achieved with the maximum pressure amplitude of oscillation, the oscillatory frequency was incrementally decreased by 1 to 2 Hz to a minimum of 5 Hz. The inspiratory/expiratory ratio was set at 0.33. During HFOV, patients were sedated and immobilised with vecuronium.

The weaning process was initiated once FIO_2 was ≤ 0.4 . MAP was gradually decreased by 1 to 2 cm H_2O and the pressure amplitude of oscillation was adjusted to maintain the $PaCO_2$ between 35 and 50 mm Hg. Extubation was considered when patient's condition had been stable for 12 to 24 h while adequate oxygenation could be maintained with an FIO_2 of ≤ 0.3 and a MAP of less than 8 cm H_2O .

Data collection

All patients were monitored with continuous arterial blood pressure measurements by indwelling catheter, continuous pulse oximetry and continuous limb lead electrocardiography. An arterial catheter was used for rapid arterial blood gas analysis. Clinical data, including invasive blood pressure, ventilator settings and arterial blood gases (PaO_2 , $PaCO_2$ and arterial oxygen saturation) were prospectively recorded prior to HFOV (0 h), at 1 h, every 4 h for 24 h and then every 8 h from 25 to 72 h of HFOV. Oxygenation index (OI) ($MAP \times FIO_2 \times 100 / PaO_2$), alveolar-arterial oxygen difference ($P(A-a)O_2$) ($FIO_2 \times (743 - 47) - (PaCO_2 / 0.8) - PaO_2$) and the PaO_2 / FIO_2 ratio were calculated at the same time intervals. At a minimum, chest radiographs were performed on CV, at 2 h of HFOV and then every 12 h and interpreted for the presence or absence of lung hyperinflation and air leak.

Statistics

Comparisons of gas exchange variables ($PaCO_2$, PaO_2 / FIO_2 ratio, OI and $P(A-a)O_2$) over time was made by the Friedman rank-sum procedure, a paired nonparametric statistic, and a two-tailed Wilcoxon matched-pairs test.

Spearman's correlation coefficient was used to study the trend of these parameters during the HFOV trial. Data are expressed as medians (ranges). Significance was defined as $P < 0.05$ for all analyses. Calculations were performed by the SPSS program (version 8.0, SPSS, Chicago, IL).

Results

The severity of respiratory failure of the patients prior to instituting HFOV (0 h) is summarised in Table 1.

Respiratory outcome on high-frequency oscillatory ventilation

The median values of maximal MAP and pressure amplitude on HFOV were 20.5 cm H_2O (range 16–26 cm H_2O) and 47.5 cm H_2O (range 35–65 cm H_2O), respectively. Median duration of FIO_2 above 0.5 was 4.5 h (range 1.5–12 h). None of our patients had oxygenation or ventilation failures on HFOV.

The $PaCO_2$ at 4 h was significantly lower than at 0 h (median 34 versus 45.5 mm Hg, $P = 0.012$, Wilcoxon matched-pairs test) and remained within the target range thereafter (median ranged between 32 and 50 mmHg). There was a significant and sustained increase ($P < 0.001$, Spearman's correlation coefficient for the whole observation period 0–72 h) in PaO_2 / FIO_2 ratio and a significant and sustained decrease ($P < 0.001$, Spearman's correlation coefficient for the whole observation period 0–72 h) in OI and $P(A-a)O_2$ throughout the course of HFOV. These improvements were achieved as early as 4 h after initiating HFOV ($P < 0.05$, Wilcoxon matched-pairs test).

The $PaCO_2$, OI, $P(A-a)O_2$ and PaO_2 / FIO_2 ratio of the patients, prior to HFOV (0 h) and at the multiple time intervals during the first 72 h of HFOV and the trends of these parameters over time are shown in Fig. 1. The three patients with pre-existing air leak did not demonstrate progression of air leak during HFOV and there was resolution of the air leak within 24 h of instituting the HFOV protocol.

Complications

Hypotension was caused by HFOV in three patients and responded rapidly to volume expansion and inotrope administration. HFOV did not induce any air leak syndrome. There were no other complications attributable to HFOV.

Outcome

Of the ten patients, eight were successfully extubated and survived to hospital discharge. The median values of length of HFOV, supplemental oxygenation and

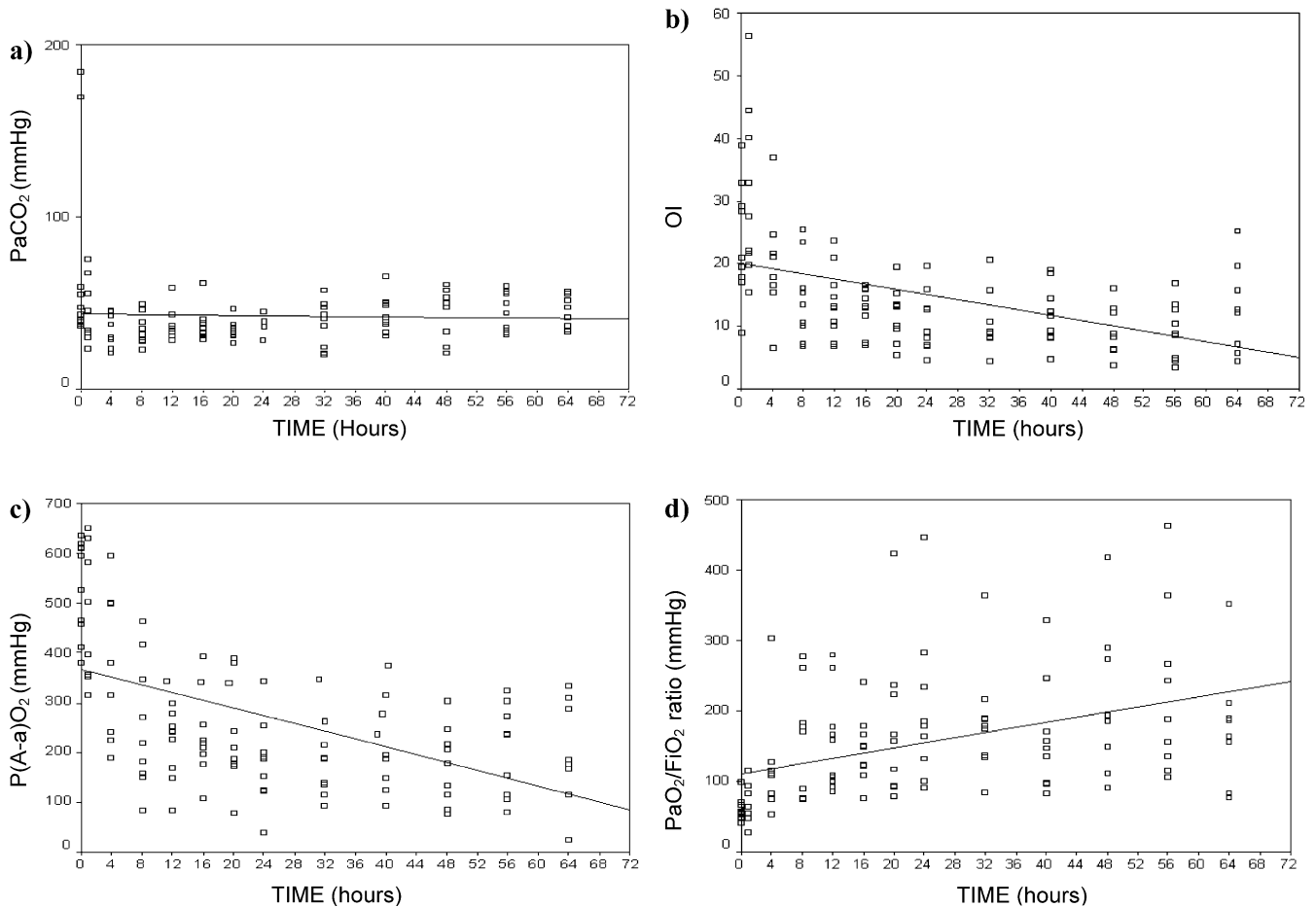


Fig. 1 Trend of PaCO_2 , OI, P(A-a)O_2 and $\text{PaO}_2/\text{FiO}_2$ ratio during the HFOV trial. HFOV was instituted at hour 0, which represents the last values of these parameters on CV just before initiation of HFOV. At hour 64, there are only nine data points (one patient died before this time). **a** Decrease in PaCO_2 was not sustained (Spearman's correlation coefficient for the whole observation period, 0–72 h). **b** Sustained decrease in OI throughout the course of HFOV ($P < 0.001$, $r = -0.53$, Spearman's correlation coefficient for the whole observation period, 0–72 h). **c** Sustained decrease in P(A-a)O_2 throughout the course of HFOV ($P < 0.001$, $r = -0.56$, Spearman's correlation coefficient for the whole observation period, 0–72 h). **d** Sustained increase in $\text{PaO}_2/\text{FiO}_2$ ratio throughout the course of HFOV ($P < 0.001$, $r = 0.53$, Spearman's correlation coefficient for the whole observation period, 0–72 h)

intensive care unit hospitalisation in the survivors were 6 days (range 3.6–16 days), 7.5 days (range 5–26 days) and 9 days (range 7–26 days), respectively. There were no deaths from respiratory failure. Two patients died of septic shock on days 2 and 6. Their $\text{PaO}_2/\text{FiO}_2$ ratios were 141 mm Hg and 133 mm Hg and their OIs were 17 and 15, immediately before death.

Discussion

The results of this study indicate that HFOV significantly improved oxygenation in a rapid and sustained fashion in paediatric patients with ARDS and relative

hypoxaemic respiratory failure on CV. During the last decade, case reports and studies of HFOV in patients failing CV strategies have demonstrated improved oxygenation and gas exchange in adult and paediatric respiratory failure [2, 4, 8, 9, 13, 14].

In this investigation, HFOV was started after a short duration of CV. This duration was less or equal to 4 h in seven patients. In the three patients who received CV for the longer periods, the duration of CV was less than 24 h in two patients. In the third patient, initially ventilated for bronchiolitis, ARDS developed 40 h after admission and the duration of CV for ARDS was only 6 h.

Eight of our ten patients (80%) treated with HFOV survived and there were no deaths from respiratory failure. HFOV was initiated as an “early rescue” therapy and the short duration of CV before HFOV most likely influenced patient survival. HFOV offers the potential to maintain adequate gas exchange without imposing large pressure changes and tidal volumes associated with ventilatory-induced lung injury. In animal studies, there is evidence that HFOV may be more effective when used early in the course of respiratory failure [6, 10]. Rosenberg and coworkers [13] suggested that the time spent receiving CV prior to institution of HFOV may be an important factor related to survival and that prolonged CV may be a poor prognostic sign for a favourable response to rescue therapies. Fedora et al. [7] also re-

ported that the duration of CV before HFOV has a substantial influence on HFOV efficacy and patient survival in children with severe acute hypoxaemic respiratory failure. In a prospective, randomised comparison of HFOV and CV in paediatric respiratory failure, Arnold et al. [3] reported that HFOV, utilising an optimal lung volume strategy, results in significant improvement in oxygenation compared with a conventional ventilatory strategy designed to limit increases in peak airway pressures. Furthermore, HFOV was associated with a lower frequency of barotraumas and improved outcome.

Two of our patients died and death was associated with sepsis in both cases. Sepsis and non-pulmonary organ failure were also associated with increased risk of death in the paediatric studies of Arnold et al. [4] and Brogan et al. [5]. Zilberberg and Epstein [16] reported that the majority of deaths from ARDS are attributable to sepsis or multiorgan dysfunction rather than primary respiratory causes.

“Early rescue” use of HFOV seems to be an effective ventilation strategy for paediatric patients with ARDS and use of this therapy should probably be considered early in the course of the disease process. However, the elective use of HFOV requires randomised trials to identify its benefits over conventional modes of mechanical ventilation and to support its routine use as a first-line therapy.

References

1. Arnold JH (2000) High-frequency ventilation in the pediatric intensive care unit. *Pediatr Crit Care Med* 1: 93–99
2. Arnold JH, Truog RD, Thompson JE, Fackler JC (1993) High-frequency oscillatory ventilation in pediatric respiratory failure. *Crit Care Med* 21: 272–278
3. Arnold JH, Hanson JH, Toro-Figuero LO, Gutierrez J, Berens RJ, Anglin DL (1994) Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 22: 1530–1539
4. Arnold JH, Anas NG, Luckett P, Cheifetz IM, Reyes G, Newth CJ, Kocis KC, Heidemann SM, Hanson JH, Brogan TV, Bohn DJ (2000) High-frequency oscillatory ventilation in pediatric respiratory failure: a multicenter experience. *Crit Care Med* 28: 3913–3919
5. Brogan TV, Bratton SL, Meyer RJ, O’Rourke PP, Jardine DS (2000) Nonpulmonary organ failure and outcome in children treated with high-frequency oscillatory ventilation. *J Crit Care* 15: 5–11
6. DeLemos RA, Coalson JJ, Meredith KS, Gerstmann DR, Null DM Jr (1989) A comparison of ventilation strategies for the use of high-frequency oscillatory ventilation in the treatment of hyaline membrane disease. *Acta Anaesthesiol Scand* 90[Suppl]: 102–107
7. Fedora M, Klimovic M, Seda M, Dominik P, Nekvasil R (2000) Effect of early intervention of high-frequency oscillatory ventilation on the outcome in pediatric acute respiratory distress syndrome. *Bratisl Lek Listy* 101: 8–13
8. Fort P, Farmer C, Westerman J, Johannigman J, Beninati W, Dolan S, Derdak S (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome—a pilot study. *Crit Care Med* 25: 937–947
9. Martinon Torres F, Rodriguez Nunez A, Jaimovich DG, Martinon Sanchez JM (2000) High-frequency oscillatory ventilation in pediatric patients. Protocol and preliminary results. *An Esp Pediatr* 53: 305–313
10. McCulloch PR, Forkert PG, Froese AB (1988) Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis* 137: 1185–1192
11. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 138: 720–723
12. Pollack MM, Ruttiman UE, Getson PR (1988) Pediatric risk of mortality (PRISM) score. *Crit Care Med* 16: 1110–1115
13. Rosenberg RB, Broner CW, Peters KJ, Anglin DL (1993) High-frequency ventilation for acute pediatric respiratory failure. *Chest* 104: 1216–1221
14. Sarnaik AP, Meert KL, Pappas MD, Simpson PM, Lieh-Lai MW, Heidemann SM (1996) Predicting outcome in children with severe acute respiratory failure treated with high-frequency ventilation. *Crit Care Med* 24: 1396–1402
15. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342: 1301–1308
16. Zilberberg MD, Epstein SK (1998) Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. *Am J Respir Crit Care Med* 157: 1159–1164