Natalie Anton
Kenneth M. Joffe
Ari R. Joffe

Inability to predict outcome of acute respiratory distress syndrome in children when using high frequency oscillation

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Abstract *Objective:* To (a) describe the experience with high-frequency oscillation (HFO) in children with acute respiratory distress syndrome (ARDS) unresponsive to conventional ventilation; (b) compare observed survival to that predicted by pediatric mortality scores and (c) determine if oxygenation index changes during HFO can predict survival.

Design: Retrospective, observational study. *Setting:* A university hospital pediatric intensive care unit.

Patients: Nineteen children with ARDS ($\text{PaO}_2/\text{FIO}_2 < 200$) unresponsive to conventional ventilation treated with HFO from January 1995 to September 1996. *Interventions:*

None. *Measurements and results:* The following were recorded: demographic, arterial blood gas and ventilator variables at the time points 0, 6, 12 and 24 h after the start of HFO; PRISM in the first 24 h of admission and pediatric respiratory failure and multiple organ system failure scores on the day of starting HFO. The mortality rate was 26% (5/19). The

survival was better than predicted by the Pediatric Respiratory Failure score ($p < 0.01$). None of the scores differentiated survivors from non-survivors ($p > 0.25$). There was no significant change in oxygenation index over the first 24 h ($p > 0.18$). Of patients with an initial oxygenation index higher than 20 who did not have at least a 20% reduction in oxygenation index by the time 6 h, 6/9 (67%) survived (sensitivity 75%, specificity 57%). *Conclusions:* Survival in pediatric ARDS patients treated with HFO could not be predicted using several outcome scores or the oxygenation index (in the first 24 h). Survival was significantly better than predicted by the Pediatric Respiratory Failure score. A prospective randomized controlled trial of HFO in ARDS is warranted.

Keywords Acute respiratory distress syndrome · High-frequency ventilation · Mechanical ventilation · Pediatrics · Respiratory failure · Ventilators, mechanical

N. Anton · K. M. Joffe · A. R. Joffe (✉)
Pediatric Intensive Care Unit,
Department of Pediatrics,
University of Alberta,
Edmonton, Alberta, T6G 2B7, Canada
e-mail: ajoffe@cha.ab.ca
Tel.: +1-780-4071673
Fax: 780 407 3214

Introduction

Acute respiratory distress syndrome (ARDS) has been the topic of much research and debate in the last number of years. The concept of ventilator-associated lung injury (VALI) has been advanced and the relative contributions of overdistention of alveoli (volutrauma), repeated opening and closing of alveoli (atelectrauma) and oxygen toxicity have been considered [1]. It is

clear in animal models that each can significantly contribute to lung injury and the pathology of ARDS [1]. It is less clear in humans what the relative role of each is and the best way to minimize their effects. Emerging data suggests that both are, indeed, important and can affect the outcome of ARDS in humans [2, 3], and the therapeutic roles of optimal PEEP and tidal volume limitation have become incorporated into common practice.

High-frequency oscillatory ventilation (HFO) is theoretically an ideal method of ventilation to limit VALI. In HFO, the lung is recruited with high mean airway pressure, kept open with this mean airway pressure and the potential for overdistention is minimized with the very small tidal volumes. The data in humans to support an improved outcome from HFO in ARDS is minimal. There are no large prospective randomized studies to confirm benefit. One small study does suggest benefit in children with ARDS [4] and another study suggests this benefit can be predicted early after the institution of HFO [5].

We undertook this study to describe the use of HFO for ARDS in our pediatric intensive care unit (PICU). We investigated whether the patients we have treated in our PICU with HFO for ARDS have had an improved outcome compared to historical controls and if this outcome could be predicted very early in their HFO course.

Materials and methods

The charts of all consecutive pediatric patients with ARDS who were treated with HFO after initial conventional mechanical ventilation (CMV) in our PICU from January 1995 to September 1996 were reviewed retrospectively. The institutional research ethics board approved the study prior to chart review and the study was conducted according to the principles established in Helsinki. The PICU is a 10-bed combined medical and surgical intensive care unit, staffed by trained pediatric intensivists, with over 800 admissions per year. ARDS was defined according to the European-American consensus conference on ARDS [6]: a $\text{PaO}_2/\text{FIO}_2$ ratio of less than 200, bilateral pulmonary infiltrates on the frontal chest radiograph, no clinical evidence of elevated left atrial pressure, a compatible predisposing condition and an acute onset.

The following demographic variables were recorded: age, sex, weight, underlying disease and operative status. Physiologic data were recorded in order to calculate the Pediatric Risk of Mortality (PRISM) score in the first 24 h of PICU admission [7], the Multiple Organ System Failure (MOSF) score [8] on the day of change to HFO, and the Pediatric Respiratory Failure (PeRF) score [9] on the day of change to HFO. The arterial blood gas results, ventilatory parameters (including FIO_2 , mean airway pressure) and oxygenation index (OI) were recorded pre-HFO and at 6, 12 and 24 h after the institution of HFO. The outcomes recorded included total number of ventilation days (CMV and HFO), survival at 28 days post-admission to PICU and complications. OI was defined as: $100 \times \text{mean airway pressure} \times \text{FIO}_2/\text{PaO}_2$.

In general, in our PICU, all patients with severe acute respiratory failure are initially managed with CMV. Our current strategy is pressure limitation (to peak inspiratory pressure (PIP) less than 35 cmH_2O) with permissive hypercapnia ($\text{pH} > 7.2$) and optimal positive end-expiratory pressure (PEEP) to achieve a goal of FIO_2 below 65% with a minimal oxygen saturation of more than 85% (and PaO_2 of > 60 torr [8 kPa]). This is to attempt to minimize ventilator-associated lung injury. Failure of CMV is considered to occur if the above parameters cannot be achieved or maintained. This strategy has evolved over the past 6 years. During the period of the study the principles of permissive hypercapnia and optimal PEEP were the same; however, the exact limits of acceptable pressure, FIO_2 and PaO_2 were in evolution. The decision to start HFO was, at times, based on clinical discretion and often early in ARDS. The reasons for converting to HFO in this study are classified as: oxygenation (severe ARDS with $\text{PaO}_2/\text{FIO}_2 \leq 100$), hyper-

capnia (ARDS with $\text{PaO}_2/\text{FIO}_2 < 150$ and $\text{PaCO}_2 > 70$ torr) or clinical discretion (ARDS in clinical progression).

HFO was performed using the SensorMedics 3100A ventilator (Yorba Linda, CA, USA). In general, in our PICU, an "open lung" approach to HFO is used, with initial mean airway pressures set slightly higher than those used during CMV. Ventilator adjustments and weaning are based on serial arterial blood gas results and chest radiographs using the same strategies of permissive hypercapnia and PaO_2 higher than 60 torr (8 kPa). Mean airway pressure is only weaned once the patient is on less than 50% FIO_2 . The delta P (amplitude) and frequency are adjusted to maintain the PCO_2 and pH targets. Patients were weaned to CMV once their lung disease improved. In general, if there was an initial response to HFO, weaning onto CMV occurred when there was chest radiograph improvement with MAP less than 17 cmH_2O on an FIO_2 below 50%.

In terms of statistical analysis, the comparison of predicted to actual survival for the three scores (PRISM, MOSF and PeRF) was calculated using Flora's z statistic [10]. Comparison of the three predictor scores in the survivor group and non-survivor group was calculated using a *t*-test for independent samples. The comparison of OI data at different time points was made using the *t*-test for paired samples. The significance level for all tests was set at *p* less than 0.05. A scatterplot of the change in OI over the first 6 h of HFO was constructed to compare this predictor to that described in the literature.

Results

Nineteen children aged 2.5 weeks to 5 years were treated with HFO after a trial of CMV for ARDS. The demographics of the patients, including age, cause of ARDS, contributing illnesses and outcomes are shown in Table 1. All patients met the criteria for ARDS with $\text{PaO}_2/\text{FIO}_2$ ratio of less than 200 (mean 82.3 ± 35.6 , median 73) at the time of change to HFO. Variables on CMV at the time of change to HFO were: PEEP 8.5 ± 3.5 cmH_2O , PIP 30.5 ± 4.7 cmH_2O , FIO_2 0.77 ± 0.18 , PaO_2 59 ± 21 torr and PaCO_2 57 ± 20 torr. The most common cause of ARDS was sepsis (6/19 patients). Patients were in the PICU for a mean of 11.1 ± 8.8 days (range 1–36 days, median 9 days) and were ventilated for a mean of 9.6 ± 8.2 days (range 3 h to 33 days, median 7 days). CMV was used for a mean of 1.6 ± 2.5 days (range 15 min to 11 days, median 2 days) prior to HFO, with HFO used for a mean of 2.8 ± 2.5 days (range 1 h to 9 days, median 2 days). The PICU mortality rate was 5/19, or 26%.

The OI values at the time points 0 h, 6 h, 12 h and 24 h on HFO are shown in Table 2. There was no statistically significant change in OI over these time periods. The prediction rule of Sarnaik et al. [5], which proposed that those patients with an initial OI of more than 20 who did not have a reduction of at least 20% in OI by 6 h on HFO can be predicted to die, had a sensitivity of 75% and a specificity of 57%. The scatterplot in Fig. 1 presents this graphically. Thus, 6/14 survivors in our study were falsely predicted to die.

The outcome relative to that predicted by the PRISM, MOSF and PeRF scores is shown in Table 3. The actual

Table 1 Demographic data for patients with acute respiratory distress syndrome treated with high-frequency oscillation

Patient	Age ^a	Outcome ^b	Cause of ARDS ^c	Contributing illness	Cause of death	PICU days	Ventilator days	HFO days	pre-HFO PaO ₂ /FIO ₂	Reason for HFO ^c
1	2.5 yr	a	Sepsis	Liver transplant	—	9	7	2	160	Clinical
2	2.5 yr	a	RSV	Liver transplant	—	9	7	4	73	Oxygenation, hypercapnia
3	5.0 yr	a	Aspiration pneumonia	—	—	13	7	1 h	100	Oxygenation
4	1.5 mo	a	Pertussis	—	—	17	14	9	74	Oxygenation, hypercapnia
5	4.5 yr	a	Sepsis	Short gut syndrome	—	23	20	7	105	Hypercapnia
6	2.5 wk	a	RSV	—	—	12	11	1.5	62	Oxygenation
7	2.0 yr	a	Aspiration pneumonia	Cerebral palsy	—	11	10	3.5	73	Oxygenation
8	6.0 mo	a	Sepsis	—	—	6	6	3	69	Oxygenation, hypercapnia
9	2.5 yr	a	RSV	West syndrome	—	6	5	2 h	74	Oxygenation
10	2.0 mo	a	RSV and sepsis	—	—	22	21	6	90	Oxygenation
11	5.0 yr	a	Pulmonary edema	Acute renal failure	—	6	5	4	35	Oxygenation, hypercapnia
12	2.5 mo	a	RSV	Prematurity, BPD	—	6	5	2	160	Clinical
13	4.0 mo	a	Sepsis	Chronic renal failure	—	36	33	4	126	Clinical
14	1.5 yr	a	Foreign body aspiration	—	—	8	6	2	95	Oxygenation
15	7.0 mo	d	Aspiration pneumonia	—	Hypoxia	1	3 h	3 h	44	Oxygenation
16	3.0 wk	d	Pertussis	—	Hypoxia	5	4	2 h	50	Oxygenation
17	1.0 yr	d	Sepsis	—	Septic shock	1	1	12 h	45	Oxygenation
18	2.5 yr	d	Sepsis	Acute liver failure	Brain herniation	3	3	1	56	Oxygenation
19	9.0 mo	d	Pulmonary hemorrhage	Pulmonary HTN	GI bleed	17	17	2.5	73	Oxygenation

^a Age in years (yr), months (mo) or weeks (wk)^b Outcome given alive (a) or dead (d)^c Classified as oxygenation (severe ARDS with PaO₂/FIO₂≤100), hypercapnia (ARDS with PaO₂/FIO₂<150 and PaCO₂>70 torr) or clinical discretion (ARDS with RSV respiratory syncytial virus, BPD bronchopulmonary dysplasia, HTN hypertension, PaO₂/FIO₂<200 and in progression)

Fig. 1 Scatterplot of the change in oxygenation index (OI) over the first 6 h of high-frequency oscillation (HFO). Patients with an OI more than 20 pre-HFO, without 20% or more reduction in OI by 6 h on HFO, are shown in the marked right upper quadrant. This rule had a sensitivity of 75% in predicting death; however, only 57% of the patients who survived had been predicted to survive. *Open circles* survivors, *closed circles* death

Table 2 Oxygenation index^a over time in the children with acute respiratory distress syndrome treated with high-frequency oscillation

Patient	Outcome ^b	OI pre-HFO	OI at 6 h	OI at 12 h	OI at 24 h
1	a	8.1	17	12	11
2	a	24.5	65	32	25.5
3	a	14	—	—	—
4	a	24	19.7	21	18
5	a	21	21	18	14.7
6	a	22	9	21	11.7
7	a	28.8	24	24	21.7
8	a	43.5	12	12.6	17
9	a	14.8	—	—	—
10	a	21.1	18.2	20.2	24.2
11	a	103	26.4	18.2	15.7
12	a	5.6	9	6.2	6.7
13	a	9.5	10.9	10.3	5.9
14	a	18.9	20.8	12.6	15.7
15	d	—	—	—	—
16	d	26	—	—	—
17	d	35.5	22.4	—	—
18	d	23.2	32.7	57.1	—
19	d	27.2	30.3	26.7	42
Mean $\pm$ SD		26.15 $\pm$ 21.3 ^c	22.56 $\pm$ 13.2 ^c	20.85 $\pm$ 12.5 ^c	17.68 $\pm$ 9.4

^a Oxygenation index (OI) calculated as: $100 \times \text{mean airway pressure} \times \text{FIO}_2 / \text{PaO}_2$; values for just prior to high-frequency oscillation (*pre-HFO*) and at 6, 12, and 24 h on HFO. Missing data points mean the patient was no longer on HFO

^b Outcome given as alive (a) or dead (d)

^c $p > 0.18$ for all comparisons, by *t*-test for paired samples

Table 3 Comparison of predicted to actual survival using three pediatric intensive care outcome scores

Score (n) ^a	Predicted mortality ^b			Survivors versus non-survivors ^c	Predicted versus observed mortality ^d
	Overall	Survivors	Non-survivors		
PRISM (19)	11.23 $\pm$ 8.3	9.1 $\pm$ 4.6	17.2 $\pm$ 13.5	ns ($p=0.25$)	$z=-2.161$, $p<0.05$
PeRF (15)	51.19 $\pm$ 23.4	51.8 $\pm$ 24.0	52.2 $\pm$ 25.9	ns ($p>0.9$)	$z=2.774$, $p<0.01$
MOSF (15)	30.96 $\pm$ 31.0	29.7 $\pm$ 27.5	33.4 $\pm$ 40.7	ns ($p>0.8$)	$z=0.261$, $p>0.10$

^a Scores used were Pediatric Risk of Mortality (PRISM), Pediatric Respiratory Failure (PeRF) and Multiple Organ System Failure (MOSF)

ⁿ Number of patients where score could be calculated

^b Given as mean percent $\pm$ SD

^c Compared by *t*-test for independent samples, all non-significant

^d Compared using Flora's *z*-statistic: a positive value indicates survival was better than predicted. Excluding the two survivors on HFO for less than 2 h does not change the results ($p<0.025$ for PRISM and PeRF)

survival was significantly worse than that predicted by the PICU admission day PRISM score. The actual survival was significantly better than predicted by the pre-HFO day PeRF ($p < 0.01$). The PRISM, MOSF and PeRF mortality predictions in the survivors were not significantly different from that of the non-survivors. The exclusion of the two survivors who were on HFO for less than 2 h did not change these results.

Discussion

The main findings of this study are that the survival in pediatric ARDS using HFO ventilation: (a) was better than in historical controls as predicted by the PeRF score, (b) could not be predicted using any of the three scores including PRISM, PeRF and MOSF and (c) could not be predicted very early in the HFO course, as suggested previously [5]. This suggests that HFO may offer a survival advantage in the management of pediatric ARDS.

Pediatric ARDS remains a difficult challenge in the PICU and several new therapies have been proposed to improve survival. The challenge remains to oxygenate and ventilate these patients adequately without causing more harm in the form of ventilator-associated lung injury (VALI). Volutrauma from overdistention of alveoli, atelectrauma from repeated opening and closing of alveoli and oxygen toxicity are the main complications associated with any form of mechanical ventilation [1]. Not only may these worsen lung injury, causing the pathologic equivalent of ARDS, they may also contribute to the systemic inflammatory response syndrome and, hence, multiple organ dysfunction syndrome [11]. Theoretically, HFO is an ideal way to recruit lung, keep it open and avoid overdistention; it allows the lung to be splinted open at a relatively constant mean airway pressure with very small tidal volumes [12].

The data for HFO used in human ARDS is scarce. There have been several reports of high-frequency ventilation used in the neonatal population with hyaline membrane disease, with the more recent trials using the "open lung" approach suggesting decreased chronic lung disease and avoidance of ECMO in some patients [13, 14, 15]. There are few pediatric reports of HFO. In 1992, Rosenberg et al. described the use of HFO after a failure of conventional ventilation in 12 pediatric patients with severe respiratory failure and showed a 58% survival rate [16]. One year later, Arnold et al. published a prospective study designed to evaluate the safety and efficacy of HFO after a trial of conventional ventilation in seven pediatric patients with respiratory failure; this study concluded that HFO can be used safely to treat respiratory failure with no compromise in hemodynamics or oxygen delivery [17].

In 1994, Arnold et al. published the only prospective randomized clinical trial of HFO in 70 children [4]. This

study showed that although there was no difference in survival, duration of mechanical ventilation or air-leak, there were fewer patients requiring supplemental oxygen at 30 days in the HFO group and a better ranked outcome in the subgroup managed with HFO only compared to those managed with CMV only. In 1996, Sarnaik et al. reported that, in a select group of 31 children treated with high-frequency ventilation (20 with HFO), the survival was 74% [5]. In adult patients, there is only one pilot study of the use of HFO in 17 patients with ARDS that suggested it is safe and produces improved gas exchange without a compromise in oxygen delivery [18]. Thus, HFO has been added to the armamentarium of therapy for ARDS based on these promising results in small numbers of patients and the theoretical advantages.

In this study the survival rate in pediatric patients with ARDS who were treated with HFO was 74% (14/19). This is much better than most reports of the mortality associated with pediatric ARDS [9, 19, 20]. Accordingly, actual survival was significantly better than that predicted by the PeRF score, which is a score that was specifically designed to estimate daily mortality risk in pediatric ARDS [9]. In addition, the PeRF and MOSF mortality predictions in the survivors were not significantly different from that of the non-survivors. That actual survival was significantly worse than predicted by the PRISM score was not unexpected, because this score is based on the first 24 h in PICU and we selected a subgroup of patients who had progressed to ARDS and a worse outcome after the first 24 h. These data suggests that HFO can improve the outcome of ARDS.

The usefulness of the OI in predicting outcome in ARDS while on HFO has been reported. Arnold et al. reported, in their prospective trial [4], that the strongest predictor of non-survival while on HFO was an OI of more than 42 at 24 h (odds ratio 20.8, sensitivity 62% and specificity 93%). In the adult pilot study [18], a pre-treatment OI of more than 47 predicted mortality with a sensitivity and specificity of 100%. In contrast, Sarnaik et al. described that, on HFO, survival could be predicted at 6 h by the change in the OI [5]. Those with an OI pre-HFO of more than 20 and failure to decrease the OI by more than 20% at 6 h could be predicted to die with a sensitivity of 88% and specificity of 83% (odds ratio 33). We were unable to confirm this prediction rule. Moreover, using this rule in our population, 6/14 survivors were falsely predicted to die. In addition, one of our survivors had an OI pre-HFO of 103 and another of 43.5. At 24 h on HFO, although there was a trend towards improving OI, there was not a statistically significant improvement in OI in our population. This may be due to the small numbers of patients at that time point. Overall, our results suggest that OI at these early time points may not be an accurate predictor of mortality in patients managed with HFO for ARDS.

It is important that the patients in our study be comparable to those of previous studies in order for the above comparisons to be valid. In our study the average OI pre-HFO was 26 ± 21 and time on CMV prior to HFO was 1.6 ± 2.5 days (range 15 min to 11 days). This is comparable to the work of Sarnaik et al. [5], where the pre-HFO OI was an average of 25 (25th percentile 19, 75th percentile 36) and the time on CMV prior to HFO was 38 ± 57 h (range 1–240 h). In the 12 patients in our study with an initial OI over 20, the reason for high OI was both MAP (20 ± 6.9) and FIO₂ (0.82 ± 0.17). This is similar to the study by Sarnaik et al., where all the patients were on an FIO₂ of 1.0 with the average MAP 20 cmH₂O (25th percentile 16 cmH₂O, 75th percentile 22 cmH₂O) [5]. In the study by Arnold et al. [4] the pre-HFO OI was 25.5 ± 9.6 , comparable to our study; the time on CMV prior to randomization to HFO was longer, with a wide range, at 143 ± 240 h. The OI in their study did not fall from pre-HFO values over the first 18 h of HFO, even in survivors [4], a finding similar to our study. Therefore, our patients were similar to those in previous studies and a comparison to the prediction rule of Sarnaik et al. [5] is likely valid. However, we cannot completely rule out that the inability to confirm the prediction rule was due to patient differences, such as their being at an earlier time point in the evolution of ARDS.

The limitations of our study must, of course, be recognized. These include its retrospective nature, the small number of patients and comparisons to historical controls, thus limiting the ability to make firm conclusions. There have been many new therapies proposed for ARDS in recent years [21, 22] and, despite initial encouraging results, they have not subsequently been confirmed to provide benefit. The list includes nitric oxide [23], surfactant [24] and partial liquid ventilation. In addition, the mortality from ARDS may be improving [25] and this would limit the usefulness of historical controls for proving benefit. A recent trial of ECMO compared to

conventional ventilation for pediatric ARDS was halted because of a better outcome than anticipated using conventional ventilation [26]. Still, despite these significant limitations, we found that predictive scores of mortality in PICU and ARDS had limited usefulness in our population and that survival was better than predicted.

These results are encouraging and warrant a multicenter prospective randomized trial to define the role of HFO early in pediatric ARDS. It would be important to compare HFO to a protocol-driven CMV strategy that is aimed at avoiding ventilator-associated lung injury; this includes low tidal volume [3] and PEEP adequate to keep ventilation on the deflation limb of the lung's pressure-volume curve, avoiding atelectrauma [27, 28]. Enrolling patient numbers adequate to have mortality as a primary end point may be difficult; surrogate outcomes may include ventilator-free days and multiple organ dysfunction scores [29].

In conclusion, this study found that the outcome of pediatric ARDS treated with HFO could not be predicted using several prediction rules, including the PeRF score, which was designed specifically for pediatric respiratory failure. Survival was significantly better than predicted by PeRF. In addition, the OI at early time points could not help predict outcome on HFO as had been suggested by others. We conclude that HFO is a promising therapy for pediatric ARDS that may improve survival. However, like the many new therapies being used for ARDS, HFO must be subjected to a large rigorous prospective, randomized, controlled trial to delineate its role. HFO may be ideally suited for early use in ARDS to prevent ventilator-associated lung injury, multiple organ dysfunction and death.

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