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THE INFLUENCE OF AN EARLY APPLICATION OF HIGH-FREQUENCY OSCILLATORY VENTILATION ON THE OUTCOME IN PAEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

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A b s t r a c t

The objective of this study was to evaluate the effect of timing in the use of high-frequency oscillatory ventilation (HFOV) on the survival of children with severe acute hypoxemic respiratory failure and ARDS who were initially on conventional mechanical ventilation (CMV). Twenty-six consecutive patients, 17 males and 9 females, fell into two groups: the early intervention group (17 patients) that received HFOV during the first 24 hs and the late intervention group (9 patients) with HFOV initiation after 24 hs of mechanical ventilation. Nine patients met extracorporeal membrane oxygenation (ECMO) criteria but only two patients were cannulated. The early use of HFOV resulted in better survival in the early intervention group (58.8% *vs* 12.5%).

K e y w o r d s

Respiratory failure, Children, High frequency oscillatory ventilation, Early intervention, Mortality

INTRODUCTION

Acute respiratory failure in both pediatric and adult patient populations have been extensively studied with a recent emphasis on ventilation strategies that can effect mortality outcome. Research in adults has focused on well-defined trials of lung protective strategies proposed on the basis of preliminary reports of their potential benefits. These strategies have included permissive hypercapnia, limited peak inspiratory pressures (PIP), high positive end-expiratory pressure (PEEP), limited tidal volumes and tracheal gas insufflation (TGI). During the past two years, reports of five randomised controlled trials of adult acute respiratory distress syndrome (ARDS) have been published or presented in which one or more of these lung protective strategies have been used *(1–4)*. The results of most of these studies have been either negative, inconclusive or from a single centre, with the exception of a recently reported, but not yet peer reviewed, high stretch-low stretch study from the National Institute of Health. This study reported

a statistically significant reduction in mortality when tidal volumes less than 6 ml/kg were used in the patients as compared to 12 ml/kg in the control group.

High frequency oscillatory ventilation has also been described as a lung protective strategy in several positive randomised controlled trials in infants and pediatric patients (*5–10*). The Arnold randomized controlled trial on paediatric ARDS, although not showing a statistically significant effect on mortality, demonstrated a statistically significant reduction in chronic lung disease in patients managed with HFOV, suggesting a lung-sparing benefit. Today in many institutions, HFOV is considered a routine therapy, a „rescue„ method in acute pediatric respiratory failure (*11,12*). *Fort et al*., in a pilot rescue trial of high frequency oscillatory ventilation (HFOV) in adult ARDS, demonstrated the ability of this approach to improve oxygenation in patients with very severe hypoxic injury (Lung Injury Score, 3.8; partial arterial oxygen tension / fraction of inspired oxygen [PaO_2/FiO_2 ratio], 77 torr) (*13*).

Because HFOV is considered to be a „rescue" intervention, it is usually used at later stages of acute respiratory failure and its proper timing has not been investigated . The aim of this study was to evaluate the effect of HFOV intervention timing on the survival of children with severe acute hypoxemic respiratory failure who were managed by lung protective strategies of conventional mechanical ventilation (CMV). This study is based on retrospective analysis of the patients treated at our departments.

MATERIALS AND METHODS

An early intervention was defined as an application of HFOV within 24 h of the decision that the patient met the entry criteria.

Patients. Twenty-six consecutive patients (mean age, 3.7 years; range 5 weeks to 24 years; *Table I*) were admitted to the Paediatric Intensive Care Unit (PICU) with severe hypoxemic respiratory failure which met the definition of ARDS and failed to respond to conventional mechanical ventilation (*14*). This group also included three older patients, aged 17, 19 and 24 years, who were admitted to the Unit to be considered for ECMO. The mean body mass was 13.8 kg (range, 2.5 to 70 kg) and there were 17 males and 9 females. In the early intervention group of 17 patients (group 1) 59% were admitted with the diagnosis of pneumonia, 12% for sepsis, 12% for trauma, and 12% for congenital diaphragmatic hernia. In the late intervention group comprising 9 patients (group 2), 44% had pneumonia and 33% were septic. The mean Paediatric Risk of Mortality score (PRISM) was 22 on admission. Six of 17 group 1 patients had air leaks while two of nine group 2 patients had air leaks. The design of the study was approved by the Institutional Review Board and written informed consent was obtained from all patients' parents.

Methods. The conventional mechanical ventilation (Siemens Servo 300, Sweden) strategy utilized in the PICU is based on the lung protective approaches described in the Introduction. The approach to improving oxygenation involves an increase in PEEP to recruit lung volume. If more than 15 cmH_2O PEEP was indicated, then the I:E ratio was increased to 1:1. If hypoxemia persisted (PaO_2 75 torr [10 kPa]), prone positioning was applied.

The protective ventilation strategies limited PIP to 30 cmH_2O and permitted hypercapnia according to the recommendation of the American College of Chest Physicians (*15*). Tidal volumes

Table 1
Patient characteristics, ventilation support and its outcomes

Patient	Gender	Weight (kg)	Age (mo)	P/F (torr)	OI	Air Leak	pre-HFOV CMV (h)	HFOV (h)	Outcome
Early Intervention									
1	F	7	11	90	27	N	9	99	Survived
2	F	70	213	66	39	Y	1	14	Died
3	M	60	228	86	40	Y	1	60	Survived
4	F	10	11	64	39	N	12	40	Survived
5	M	5	2	98	13	N	5	48	Survived
6	F	4.5	5	78	14	N	10	92	Survived
7	M	4.5	1.5	136	11	N	11	74	Survived
8	M	6	5	101	11	N	12	24	Survived
9	M	4.7	3	71	14	Y	12	83	Survived
10	M	4	4	52	57	N	20	202	Died
11	M	50	156	48	52	N	17	5	Died
12	M	7	5	96	18	Y	3	192	Died
13	F	28	288	92	23	N	22	121	Died
14	M	7	10	47	45	Y	0	147	Died
15	M	4	3	94	16	N	10	85	Survived
16	F	3	1.2	105	20	Y	0	13	Died
17	M	3.8	1.2	95	17	N	5	82	Survived
Late Intervention									
1	M	7	11	55	40	Y	66	39	Died
2	F	27	109	45	58	N	46	18	Died
3	M	2.5	1.2	95	7	N	592	144	Died
4	M	2.6	2	49	41	N	141	192	Died
5	F	18	48	120	15	N	125	12	Died
6	M	5.5	6	111	27	N	76	172	Died
7	F	12	30	53	59	N	34	42	Died
8	M	4	1.2	79	41	N	37	120	Survived
9	M	2.7	2	101	9	Y	83	84	Died

Legend: F – female; M – male; mo – months; OI – oxygenation index at time of transition to HFOV; P/F – PaO2/FiO2 ratio at time of transition to HFOV; pre-HFOV CMV – conventional mechanical ventilation before high frequency oscillatory ventilation; h – hours; Y – yes; N - no.

were kept below 7 ml/kg and, in severe ARDS, as low as 3 ml/kg. If $PaCO_2$ was 75 torr [10 kPa] and/or pH was below 7.2, tracheal gas insufflation (TGI) was used to reduce dead space and improve alveolar ventilation. An indication for transition to HFOV was the use of FiO_2 0.6 and the mean airway pressure (Paw) 15 cmH_2O to maintain oxygen saturation greater than 89% or hypercapnia ($PaCO_2$ 75 torr [10 kPa]) and/or acidosis (pH 7.20) with the use of the strategies described.

HFOV was instituted using an electronically driven, active exhalation oscillator (SensorMedics 3100A, USA) with an „Optimal Lung Volume“ approach, as previously described, to recruit the alveoli and maintain lung inflation above the alveolar closing volume (*10*). The initiation of HFOV was with Paw set 2 to 5 cmH_2O above the last Paw on CMV and then gradually increased in 1– to 2-cmH_2O increments to improve oxygenation until there was no further improvement in saturation by pulse oximetry, or there were no signs of lung hyperinflation, as indicated by the diaphragm position beyond the 9^{th} rib on the chest film. In response to improving oxygenation, FiO_2 was decreased to 0.6 or below. In the presence of air-leak, Paw was decreased approximately 1 to 2 cmH_2O below the optimal lung volume and FiO_2 0.6 was tolerated to maintain saturation 85% for 12 to 24 hours or until resolution of the air-leak occurred. Patients who failed to respond to HFOV following attempts to optimise lung recruitment and showed persistent hypoxemia were offered ECMO unless contraindicated.

Ventilator frequency was set at 10 Hz in infants, 5 to 10 Hz in older children and less than 5 Hz in patients weighing more than 30 kg. The pressure amplitude (Delta-P) was initially increased until adequate chest wall movement was detected and then adjusted to maintain $PaCO_2$ within acceptable limits (< 53 torr [7 kPa]). Reduction in PaCO2 was controlled by increasing Delta-P by steps of 2 to 5 cmH_2O. A failure to adequately respond to increases in Delta-P were treated by decreasing the ventilator frequency by 1 to 2 Hz.

Weaning from HFOV was uniform in all patients with decreasing Paw gradually in 1 to 2 cmH_2O increments as allowed by the oxygen saturation, and Delta-P in 2 to 5 cmH_2O increments according to $PaCO_2$. Transition back to CMV was considered when the patient was on HFOV settings of Paw 15 to 20 cmH_2O, FiO_2 0.6, and did not desaturate during airway suctioning as well as having resolved air-leak and/or improved chest X-rays. Patients were switched back to CMV in Volume Support mode and at the Paw and FiO_2 as during HFOV.

The patients were stratified for analysis by the hours of conventional mechanical ventilation prior to HFOV intervention. Group 1, the early intervention group, included patients who were treated with mechanical ventilation for 24 hours. Group 2, the late intervention group, included patients transitioned to HFOV after the first 24 hours of CMV.

The statistical analysis examined patients' characteristics on admission, duration of all modes of ventilation, ventilation and oxygenation indices as well as outcomes for both groups of patients. The means of the parameters studied were evaluated using unpaired Student's t-test with a *P* value of 0.05 taken as statistically significant.

RESULTS

Table 2 summarizes the mean data of the stratified groups at time of intervention with HFOV. There were no statistical differences in weight, age or PRISM score on admission although the early intervention group tended to be older and had a higher average body mass. There were also no differences in the $AaDO_2$, PaO_2/FiO_2 ratio or oxygenation index (OI) between the groups at the time of HFOV intervention. The early intervention group was by definition in more of the acute first 24 hour stabilization period transitioning to HFOV and had statistically significantly more hypercapnia with associated acidosis and had slightly better oxygenation.

Table 2
Comparison of the early and late intervention groups

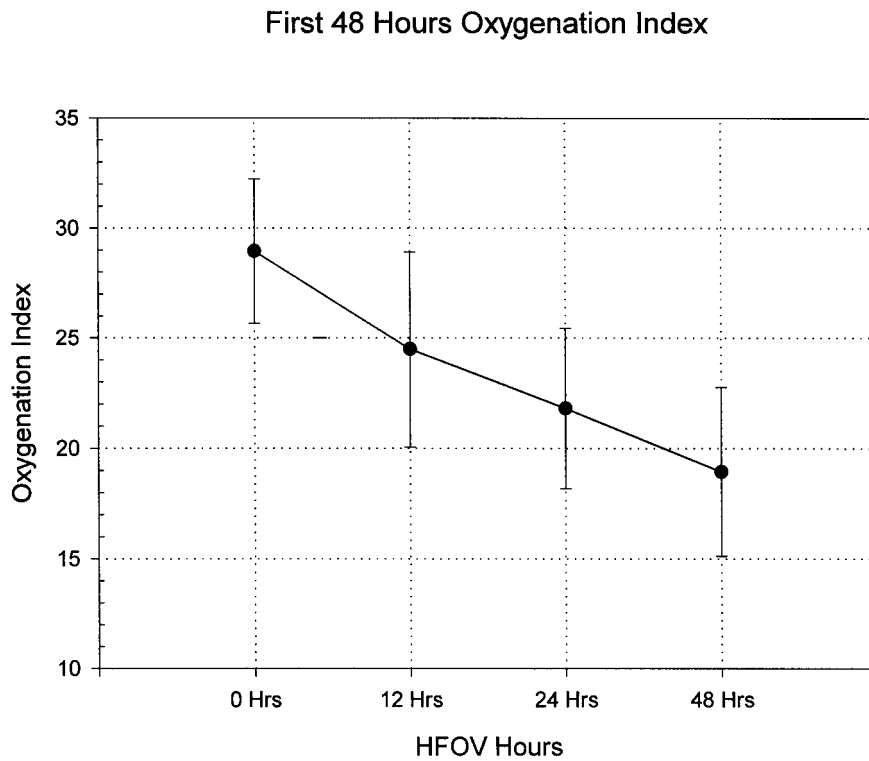
Parameter	Early Intervention (n=17)	Late Intervention (n=9)	Significance p-value
Age (months)	55.7	23.4	0.351
Weight (kg)	16.4	9.0	0.345
pH	7.180.18	7.400.08	0.003
PaO2 (torr)	5510	507	0.038
PaCO2 (torr)	8629	5714	0.012
AaDO2 (torr)	421122	413177	0.443
PaO2/FiO2 (torr)	8323	7927	0.328
OI	2715	3318	0.190
PRISM	21.8	22.0	0.947
Duration of CMV pre-HFOV (hours)	8.8	133.3	0.007
Duration of HFOV (hours)	81.2	91.4	0.693
Duration of CMV post-HFOV (hours)	132.2	26.2	0.089
Duration of total MV (hours)	222.3	251.0	0.721
30 Day survival rate	10 (58.8%)	1 (12.5%)	0.010

AaDO2 – alveoloarterial oxygen difference; OI – oxygenation index; PRISM – Pediatric Risk of Mortality Score; HFOV – high frequency oscillatory ventilation; CMV pre-HFOV – conventional mechanical ventilation before HFOV; CMV post-HFOV – conventional mechanical ventilation after HFOV; MV – mechanical ventilation.

Fig. 1 presents the time course of oxygenation response, expressed as the oxygenation index, during the first 48 hours of HFOV for all the patients. The OI decreased by 15 % during the first 12 hours and continued to improve during the next 36 hours. The ventilation response to HFOV was very rapid, with clinically significant improvement in pH and $PaCO_2$ within two hours of HFOV initiation.

The overall survival rate was 42% (11/26 patients). There was a statistically significant difference in 30-day mortality (p=0.010) between group1 and group 2 (58.8% versus 12.5%) (*Table 2*). All deaths were due to multi-organ system failure and irreversible, profound hypoxemia.

Fig. 1
Oxygenation index during the first 48 hours



The mean(SEM) value of oxygenation index during first 48 hours of HFOV. Time 0 represents the last physiologic measurement before enrolment.

There were no differences between the groups in the duration of management with HFOV, post-HFOV mechanical ventilation or the total length of mechanical ventilation. The last two factors were related to the high mortality in group 2 in which two-thirds of patients died within the first 48 hours of HFOV initiation. Survival to discharge in the early intervention group was 47% with two of the deaths beyond 30 days following weaning from mechanical ventilation. The sole survivor in the late intervention group survived to hospital discharge. Air leak was associated with a higher mortality with two-thirds of the early intervention patients with air leak expiring and 100% of the late intervention patients with air leak.

In group 1, eight patients met the ECMO criteria. Five patients had ECMO contraindications due to disseminating intravascular coagulopathy or acute myeloblastic leukemia and pancytopenia and all of these patients died. One patient was cannulated for ECMO but died due to uncontrollable bleeding. The remaining two patients were adequately managed with HFOV and were not placed on ECMO. In group 2, only one patient was treated with ECMO and died during this treatment. In the rest of the patients, ECMO was contraindicated due to the duration of CMV prior to HFOV.

DISCUSSION

This retrospective study of pediatric patients with acute hypoxic respiratory failure is the first insight into the effect of the duration of CMV prior to initiation of HFOV on the patient survival. The statistically significant differences in mortality related to the duration of lung protective conventional mechanical ventilation prior to HFOV may raise questions as to the benefits of these protective approaches or stimulate a discussion on the benefits of HFOV in protecting the lung architecture from time-dependent, ventilator-induced lung injury (VILI).

ARDS is a multi-phase process and the sequence of changes from the exudative to proliferative and fibrotic stages reflect a cascade of events that build up one upon another. The markers associated with VILI are also time dependent and include protein leak, surfactant deactivation, atelectasis, hyaline membrane formation, mediator activity, interstitial fibrosis, hypoxic death, and multi-organ system failure (MOSF).

Beginning with large swings in alveolar volume and pressures, the pressure on the alveolar capillary changes significantly on each breath. This constant flexing of the capillary may be primarily responsible for stress fractures of the capillary bed, leading to protein leak. *Hotchkis, et al*. (*16*) have suggested that it is not only the amplitude of the pressure swing, but also the frequency of swings that may be responsible for an increase in capillary fractures. This is also supported by the study in ringtail monkeys by *Jackson* where he reported significant reductions in alveolar protein volume when HFOV (12 %) was compared to CMV (27 %) (*17*).

The impact of proteinacious material on the alveolar space is the effects it has on surfactant function. Proteinacous materials deactivate the surfactant, rapidly converting a large-aggregate, functional surfactant into a small-aggregate, non-functional surfactant. *Lewis et al.* has demonstrated in several studies that the use of large tidal volumes is associated with rapid conversion of large-aggregate to small-aggregate, non-functional surfactants. They have also reported significant protection of aggregate size with the use of HFOV in their group (*18*). *Froese et al. (19)* has also demonstrated enhanced surfactant function and better preservation with HFOV.

The loss of surfactant function is directly related to alveolar instability, alveolar derecruitment, atelectasis and is associated with increased levels of mediator release. Statistically significant differences in TNF-alpha, thromboxane and neutrophil activation have been reported by *Takata et al.*(*20*)*, Imai et al.* .(21), Sigiura et al.(22). and *Gunnarsson et al.*(*23*) when conventional strategies were compared with HFOV. Several mediators, e.g., IL-1 and IL-8, are responsible for the attraction of collagen forming cells to the lung, which results in fibrotic lesions. In a baboon model of prematurity, *Coalson et al.* (*24*) have demonstrated a 40 percent reduction in lung tissue volume when conventionally ventilated, premature baboons were compared to HFOV treated animals. In a trial involving premature infants (*5, 6*) as well as in a paediatric randomized controlled trial (*10*), statistically significant reductions in chronic lung disease were reported in ARDS when HFOV was used.

Elevated oxygenation to treat atelectasis has also been associated with increased mediator release that may exacerbate biochemical injury. A release of these mediators from the lungs into the blood stream provides a distribution pathway to other organ systems and may contribute to multi-organ system failure (*25*), the cause of all deaths in this study. Lung protective strategies may serve to protect other organ systems as well.

The use of HFOV, as a theoretically optimal lung protective strategy which provides ability to recruit more alveoli with a constant, high distending pressure that minimizes capillary pressure swings and enables control of carbon dioxide with minimal alveolar volume swings, may interrupt the timed VILI sequence of events.

Lung protective strategies based on conventional ventilation may not be as protective as HFOV. As long as bulk-flow tidal volumes are required to remove carbon dioxide, pressure and volume swings achieved with conventional ventilation will be higher than those with HFOV. Additionally, at the same mean airway pressure, the lowest pressure that holds the alveoli open will be higher with HFOV than with low stretch techniques using conventional ventilators and, therefore, lower derecruitment will occur (*26–28*). *Nakagawa et al.* (*28*) has reported that as long as PIP is less than the upper inflection point, the lung will derecruit even at higher PEEP levels *(28).* The sum of these effects may account for the differences in mortality we found with an early use of HFOV.

The duration of conventional mechanical ventilation before HFOV has a substantial influence on HFOV efficacy and patient survival in children with severe acute hypoxemic_respiratory failure. This report is to suggest that the use of HFOV as „salvage therapy“ is of little benefit to pediatric patients who have already developed hypoxemic respiratory failure. The use of this therapy should be considered early in the course of treatment of any pediatric patient meeting definition of ARDS. A randomized controlled trial of early use of HFOV versus conventional ventilation may answer this question more definitely.

A c k n o w l e d g m e n t

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VLIV ČASNÉ APLIKACE VYSOKOFREKVENČNÍ OSCILAČNÍ VENTILACE NA PŘEŽITÍ PEDIATRICKÝCH PACIENTŮ SE SYNDROMEM AKUTNÍ RESPIRAČNÍ TÍSNĚ

S o u h r n

Cílem této retrospektivní analysy bylo zjistit vliv doby, kdy byla HFOV použita, na přežití dětí se závažným akutním hypoxemickým respiračním selháním, které byly ventilovány konvenční mechanickou ventilací (CMV) s protektivní plicní strategií. Pediatrická jednotka intensivní péče v universitní dětské nemocnici, která poskytuje služby regionu se zhruba 2 miliony obyvatel a jako jediné ECMO centrum v České republice poskytuje služby 10 milionům obyvatel.

Práce popisuje dvacet šest pacientů starších než 1 měsíc se závažným hypoxemickým selháním a ARDS, kteří byli napojeni na HFOV. Průměrný věk byl 3.7 roku, soubor zahrnuje i 3 starší pacienty, kteří byli léčeni na našem pracovišti (17, 19 a 24 let). Průměrná váha byla 13.8 kg, 17 chlapců a 9 dívek. Devět pacientů splňovalo kriteria extrakorporální membránové oxygenace (ECMO), pouze 2 pacienty bylo nutno kanylovat. Po příjmu byli pacienti ventilováni protektivní plicní strategií tlakově řízenou ventilací (PCV) nebo tlakově řízenou objemově kontrolovanou ventilací (PRVC) s limitovaným maximálním tlakem v dýchacích cestách (PIP), vysokým tlakem na konci expiria (PEEP) a permisivní hyperkapnií. Pokud dosáhlo PaCO2 75 torr [10.0 kPa] a/nebo pH kleslo pod 7.20, zavedli jsme tracheální insuflaci plynu (TGI). Pokud bylo nutné použít FiO2 > 0.6 a střední tlak v dýchacích cestách (Paw) přesáhl 15 cmH2O a saturace periferní krve kyslíkem byla pod 90% nebo pokud hyperkapnie a/nebo acidosa přetrvávaly na CMV s TGI, byli pacienti přepojeni na HFOV. Při HFOV byla použita „Optimal Volume Strategy“ ke znovuotevření (recruitmentu) alveolů a optimalisaci plicního objemu. Pacienti byli přepojeni zpět na CMV pokud dosahovali Paw 15 – 20 cmH2O, FiO2 < 0.6, nebyl přítomen air-leak a/nebo bylo patrné zlepšení na rtg snímku plic a nedesaturovali při odsávání. Pacienti byli napojeni na ECMO v případě, kdy hypoxemie přetrvávala na HFOV a ECMO nebylo kontraindikováno.

Pacienti byli rozděleni do skupin podle doby napojení na HFOV. Časná aplikace byla definována jako napojení na HFOV do 24 hodin CMV (17 pacientů) a pozdní aplikace nad 24 hodin CMV (9 pacientů). Pro obě skupiny pacientů jsme zaznamenávali demografická data (pohlaví, věk, váhu, příjmové PRISM skore), dobu jednotlivých typů ventilace, oxygenační index a výsledky léčby.

Závažnost respiračního selhání v době napojení na HFOV byla srovnatelná u obou skupin pacientů (PaO2/FiO2 83 vs. 79 torr, oxygenační index 27 vs. 33, AaDO2 421 torr [56 kPa] vs. 413 torr [55 kPa]). Bez rozdílů mezi oběma skupinami byly průměrný věk, váha, příjmové PRISM skore, délka HFOV, délka CMV po HFOV (CMV post-HFOV) a celková doba ventilace. Statisticky významné rozdíly byly v mortalitě: ve skupině časné aplikace přežilo 58.8% pacientů, zatímco ve skupině pozdní aplikace jen 12.5% pacientů. Přežití v celém souboru pacientů bylo 42% (11/26 pacientů). Časné použití HFOV v prvních 24 hodinách akutního hypoxemického respiračního selhání je spojeno s lepším přežitím. Použití HFOV by mělo být zváženo v úvodu terapie každého pediatrického pacienta, který splňuje definice respiračního selhání.

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