# EFFECT OF EARLY INTERVENTION OF HIGH-FREQUENCY OSCILLATORY VENTILATION ON THE OUTCOME IN PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

FEDORA M, KLIMOVIC M, SEDA M, DOMINIK P, NEKVASIL R

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

**Abstract**

**Fedora M, Klimovic M, Seda M, Dominik P, Nekvasil R:**
**Effect of early intervention of high-frequency oscillatory ventilation on the outcome in pediatric acute respiratory distress syndrome**
**Bratisl Lek Listy 2000; 101 (1): 8–13**

***Background:*** **Acute respiratory failure in both pediatric and adult patient populations has been extensively studied with recent emphasis on ventilation strategies that can effect mortality outcome. This research in adults has focused on definitive trials of lung protective strategies that have been proposed following preliminary reports of their potential benefits. High frequency oscillatory ventilation has also been described as a lung protective strategy. For many institutions HFOV is today considered a routine therapy as a "rescue" method in acute pediatric respiratory failure.**
**Because HFOV is considered to be a "rescue" therapy, intervention with HFOV is usually in the later stages of acute respiratory failure and consideration of the time to intervention has not been previously examined.**
***Objective:*** **To evaluate the effect of time to intervention with high-frequency oscillatory ventilation (HFOV) on the survival of children with severe acute hypoxemic respiratory failure who were managed with lung protective strategies on conventional mechanical ventilation (CMV).**
***Methods:*** **Twenty-six consecutive patients older 1 month of age with severe hypoxemic respiratory failure and ARDS who at some point in their management were treated with HFOV were evaluated. The mean age was 3.7 years and included three patients treated in the Pediatric Intensive Care Unit (17, 19 and 24 years). Mean weight was 13.8 kg and there were 17 males and 9 females. Nine patients met Extracorporeal Membrane Oxygenation (ECMO) criteria, although only two patients were cannulated.**

Pediatric Intensive Care Unit, Department of Anesthesiology and Critical Care, University Children's Hospital, Masaryk University, Brno. mfedor@med.muni.cz
**Address for correspondence:** M. Fedora, MD, Pediatric Intensive Care Unit, Department of Anesthesiology and Critical Care, University Children's Hospital, Masaryk University, Cernopolni 9, CZ-662 63 Brno, Czech Republic. Phone: +420.5.4512 2404, Fax: +420.5.4512 2252

Abstrakt

Fedora M., Klimovič M., Šeda M., Dominik P., Nekvasil R.:
Vliv časné aplikace vysokofrekvenční scilační ventilace na přežití pediatrických pacientů se syndromem akutní respirační tísně
Bratisl. lek. Listy, 101, 2000, č. 1, s. 8–13

*Úvod:* Akutní respirační selhání u pediatrických i dospělých pacientů je důkladně studováno s důrazem na strategii ventilace, která může ovlivnit mortalitu. Tento výzkum se u dospělých pacientů zaměřil na studie zabývající se protektivní ventilací plic, které probíhají poté, co předběžné výsledky ukázaly jejich možný benefit. Vysokofrekvenční oscilační ventilace (HFOV) je definována jako protektivní plicní ventilace. Na mnoha pracovištích je dnes rutinně používana jako !rescue,, metoda v akutním respiračním selhání.
Protože HFOV se považuje za "rescue" terapii, používá se obvykle později v průběhu akutního respiračního selhání a nebyl tedy studován vliv doby použití HFOV.
*Cíl práce:* 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.
*Metody:* Práce popisuje 26 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 $PaCO_2$ >75 torr (10,0 kPa) a/nebo pH kleslo pod 7.20, zavedli

Anesteziologicko-resuscitační oddělení Fakultní nemocnice Brno, Fakultní dětská nemocnice J.G. Mendela, Masarykova univerzita, Brno
**Adresa:** MUDr. M. Fedora, Anesteziologicko-resuscitační oddělení FN Masarykovy univerzity, Černopolní 9, 662 63 Brno, Česká republika.

**Upon admission to the PICU, patients were initially managed with lung protective strategies using Pressure Controlled Ventilation (PCV) or Pressure Regulated Volume Control (PRVC) modes with limited peak inspiratory pressure, high positive end-expiratory pressure, and permissive hypercapnia. If a $PaCO_2$ reached >75 torr (10.0 kPa) and/or pH<7.20, tracheal gas insufflation (TGI) was instituted. If $FiO_2$ remained above 0.6 and mean airway pressure (Paw) exceeded 15 $cmH_2O$ in order to maintain arterial saturation above 89 % or if hypercapnia and/or acidosis on CMV with TGI persisted, the patients were switched to HFOV. An "Optimal Volume Strategy" with HFOV was utilized to recruit alveoli and optimize lung volume. Patients were returned to CMV when their mean airway pressure were between 15 and 20 $cmH_2O$, $FiO_2$<0.6, had no evidence of air-leak and/or improved chest X-rays, and did not desaturated during airway suctioning. Patients were offered ECMO if the hypoxemia persisted on HFOV and there were no contraindications to its use.**

**The patients were stratified for analysis by the time to intervention with HFOV. Early intervention was defined as within the first 24 hours of mechanical ventilation (17 patients) and late intervention defined patients beyond 24 hours (9 patients). Demographic data (gender, age, weight, admission PRISM score), time of each mode of ventilation, oxygenation indices and outcomes were recorded for both groups of patients.**

***Main results:*** **The severity of respiratory failure at the time of HFOV intervention was comparable in both early and late groups ($PaCO_2/FiO_2$ 83 vs. 79 torr, oxygenation index 27 vs. 33, $AaDO_2$ 421 torr (56 kPa) vs. 413 torr (55 kPa)). There were no differences in mean age, weight, admission PRISM score lenght of HFOV, lenght of CMV after HFOV (CMV post-HFOV) and the total duration of mechanical ventilation between the groups. We found a statistically significant difference in mortality with 58.8 % of the early intervention patients surviving while only 12.5 % of the late intervention patients survived. The overall survival rate was 42 % (11/26 patients).**

***Conclusion:*** **Early use of HFOV within the first 24 hours of acute hypoxic respiratory failure in pediatric patients is associated with better survival. Use of this therapy should be considered early in the course of treatment of any pediatric patient meeting this definition.** ***(Tab. 2, Fig. 1, Ref. 28.)***

**Key words: high frequency oscillatory ventilation, early intervention, late intervention, respiratory failure, acute respiratory distress syndrome, children, mortality.**

jsme tracheální insuflaci plynu (TGI). Pokud bylo nutné použít $FiO_2$ >0,6 a střední tlak v dýchacích cestách (Paw) přesáhl 15 $cmH_2O$ a saturace periferní krve kyslíkem byla pod 90 % nebo pokud hyperkapnie a/nebo acidóza přetrvávaly na CMV s TGI, byli pacienti přepojeni na HFOV. Při HFOV byla použita „Optimal Volume Strategy" ke znovuotevření (recruitmentu) alveolů a optimalizaci plicního objemu. Pacienti byli přepojeni zpět na CMV, pokud dosahovali Paw 15—20 $cmH_2O$, $FiO_2$<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 případů) a pozdní aplikace nad 24 hodin CMV (9 pacientů). Pro obě skupiny pacientů jsme zaznamenávali demografická data (pohlaví, věk, váhu, příjmové PRISM skóre), dobu jednotlivých typů ventilace, oxygenační index a výsledky léčby.

*Výsledky:* Závažnost respiračního selhání v době napojení na HFOV byla srovnatelná u obou skupin pacientů ($PaO_2/FiO_2$ 83 vs. 79 torr, oxygenační index 27 vs. 33, $AaDO_2$ 421 torr (56 kPa) vs. 413 torr (55 kPa)). Bez rozdílů mezi oběma skupinami byly průměrný věk, váha, příjmové PRISM skóre, 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).

*Závěr:* 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. *(Tab. 2, obr. 1, lit. 28).*

Klíčová slova: vysokofrekvenční oscilační ventilace, časná aplikace, pozdní aplikace, respirační selhání, acute respiratory distress syndrome, děti, mortalita.

Acute respiratory failure in both pediatric and adult patient populations have been extensively studied with recent emphasis on ventilation strategies that can effect mortality outcome. This research in adults has focused on definitive trials of lung protective strategies that have been proposed following 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 randomized controlled trials in adult ARDS have been published or presented which have used one or more of these lung protective strategies (1—4, Brower et al., in press). The results of most of these studies have been either negative. single center or inconclusive with the exception of the recently reported, but not yet peer reviewed, National Institute of Health's high stretch-low stretch study. This study reported a statistically significant reduction in mortality with the use of tidal volumes less than 6 ml/kg as compared to 12 ml/kg in the control group.

High frequency oscillatory ventilation has also been described as a lung protective strategy with several positive randomized controlled trials in infants and pediatrics (5—10). The Arnold randomized controlled trial in pediatric ARDS, although not showing a statistically significant effect on mortality, demontrated a statistically significant reduction in chronic lung disease in patients managed with HFOV, suggesting a lung sparing benefit. For many institutions HFOV is today considered a routine therapy as a "rescue" method in acute pediatric respiratory failure (11, 12). Fort et al. in a pilot rescue trial of HFOV in adult ARDS, demonstrated its ability to improve oxygenation in patients with very severe hypoxic injury (Lung Injury Score 3.8, $PaO_2/FiO_2$ ratio 77 torr) (13).

Because HFOV is considered to be a "rescue" therapy, intervention with HFOV is usually in the later stages of acute respira-

tory failure and consideration of the time to intervention has not been previously examined.

## Materials and methods

*The aim of the study:* To evaluate the effect of time to intervention with high-frequency oscillatory ventilation (HFOV) on the survival of children with severe acute hypoxemic respiratory failure who were being managed with lung protective strategies on conventional mechanical ventilation (CMV). Early intervention was defined as the application of HFOV within the first 24 hours of patients meeting entry criteria.

*The type of the study:* Retrospective analysis.

*Patients:* Twenty-six consecutive patients (Table 1) between 5 weeks and 24 years of age (mean 3.7 years) were admitted to our PICU with severe hypoxemic respiratory failure meeting the definition of ARDS and failing conventional ventilation (14). The patient population included three older patients, ages 17, 19 and 24 years, who were admitted to the PICU for consideration of ECMO. The mean weight was 13.8 kg (range 2.5 to 70 kg) and there were 17 males and 9 females. Fifty-nine percent of the early intervention group (group 1) had admitting diagnoses of pneumonia, 12 % were admitted for sepsis, 12 % for trauma, and 12 % for congenital diaphragmatic hernia. In the late intervention group (group 2), 44 % of the patients had pneumonia and 33 % were septic. Mean admission PRISM scores were 22. Six of the seventeen group 1 patients had air leaks while two of the nine group 2 had air leaks. The design of the study was approved by the Institutional Review Board and written parental informed consent was obtained from all patients.

*Methods:* The conventional mechanical ventilation (Siemens Servo 300, Sweden) strategy utilized in our PICU is based upon the lung protective approaches described in the introduction. The approach to improve oxygenation is with increases 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 ($PaCO_2$<75 torr (10 kPa)), prone positioning was applied.

Protective ventilation strategies limited PIP to 30 $cmH_2O$ and permitted hypercapnia according to recommendation of American College of Chest Physicians (15). Tidal volumes were kept below 7 ml/kg and ranged as low as 3 ml/kg in severe ARDS. If $PaCO_2$>75 torr (10 kPa) and/or pH were below 7.20, tracheal gas insufflation (TGI) was used to reduce dead space and improve alveolar ventilation. Indication for transition to HFOV was the use of $FiO_2$>0.6 and Paw>15 $cmH_2O$ to maintain an 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 with an electronically driven, active exhalation oscillator (SensorMecics 3100A, USA) using a "Optimal Lung Volume" approach as previously described to recruit the alveoli and maintain above the alveolar closing volume (10). Initiation of HFOV was with the mean airway pressure (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 signs of lung hyperinflation as indicated by the diaphragm beyond the 9th rib on the chest film. $FiO_2$ was decreased in response to improving oxygenation to 0.6 or below. In the presence of air-leak, Paw was decreased approximately 1 to 2 $cmH_2O$ below optimal lung volume and an $FiO_2$>0.6 was tolerated to maintain saturation > 85 % for 12 to 24 hours or until the resolution of the air-leak. Patients who failed to respond to HFOV following attempts to optimize lung recruiment and demonstrated persistent hypoxemia, were offered ECMO unless contraindicated.

**Tab. 1. Patient demographics, ventilation hours and outcomes.**
**Tab. 1. Demografie pacienů, hodiny ventilace a výsledek léčby.**

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

Legend: mo – months; OI – oxygenation index at time of transition to HFOV; P/F – $PaO_2/FiO_2$ ratio at time of transition to HFOV; pre-HFOV CMV – conventional mechanical ventilation before high frequency oscillatory ventilation; h – hours.

Ventilator frequency was set at 10 Hz in infants, 5 to 10 Hz in older children and <5 Hz was used in patients weighing more than 30 kg. 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 $PaCO_2$ was controlled by increasing Delta-P by steps of 2 to 5 $cmH_2O$. Failure to adequately respond to increases in Delta-P were treated by decreasing 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.

Patients were stratified for analysis by the hours of conventional mechanical ventilation prior to HFOV intervention. Group 1 (17 patients), the early intervention group, included patients who were treated with mechanical ventilation for ≤24 hours. Group 2 (9 patients), the late intervention group, included patients transitioned to HFOV after the first 24 hours of CMV.

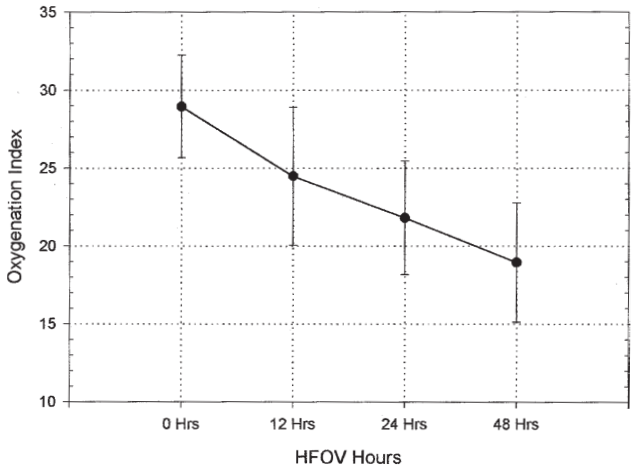


**Fig. 1. First 48 hours Oxygenation Index.**
**Obr. 1. Oxygenační index během prvních 48 hodin.**

**Tab. 2. Demographic data, mean values at time of transitioning to HFOV, lenghts of ventilation and survival in both groups.**
**Tab. 2. Demografická data, průměrné hodnoty v době přepojení na HFOV, délky ventilací a přežití u obou skupin.**

| *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 | 7.18±0.18 | 7.40±0.08 | **0.003** |
| $PaO_2$ (torr) | 55±10 | 50±7 | **0.038** |
| $PaCO_2$ (torr) | 86±29 | 57±14 | **0.012** |
| $AaDO_2$ (torr) | 421±122 | 413±177 | 0.443 |
| $PaO_2/FiO_2$ (torr) | 83±23 | 79±27 | 0.328 |
| OI | 27±15 | 33±18 | 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** |

Legend: $AaDO_2$ – 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.

The statistical analysis examined entering demographics, duration of all modes of ventilation, ventilation and oxygenation indices as well as outcomes for both groups of patients. The means of the studied parameters were evaluated using unpaired Student's t-test with statistical significance defined at $p<0.05$.

## 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 admitting PRISM score although the early intervention group tended to be older and heavier. There were also no differences in the $AaDO_2$, $PaO_2/FiO_2$ ratio or Oxygenation Index (OI) between the groups at 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.

Figure 1 presents the time course of oxygenation response during the first 48 hours of HFOV for all patients as represented by the Oxygenation Index. Oxygenation Index decreased by 15 percent during the first 12 hours and then exhibited a continued improvement during the next 36 hours. Ventilation response to HFOV was also very rapid with clinically significant improvement in pH and $PaCO_2$ within two hours after initiating HFOV.

Overall survival rate was 42 % (11/26 patients). There was a statistically significant differences in 30 day mortality ($p=0.010$) between the groups with a survival rate in the early intervention group of 58.8 % versus 12.5 % in late intervention group (Tab. 2). All deaths were the result of multi-organ system failure and irreversible profound hypoxemia.

There were no differences between the groups in lenght of management with HFOV, duration of post HFOV mechanical ventilation nor total time of mechanical ventilation. The last two factors were related to the high mortality in the late intervention group with two-thirds of them expiring within first 48 hours of HFOV. 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.

Of the 17 patients in the early intervention group, 8 patients met ECMO criteria. ECMO was contraindicated in five patients due to disseminating intravascular coagulopathy or AML and pancytopenia and all of these patients died. One patient was cannulated for ECMO but expired due to uncontrollable bleeding. The remaining two patients were adequately managed with HFOV and were not placed on ECMO. In the late intervention group only one patient was treated with ECMO and expired during treatment. ECMO was contraindicated in the balance of this group due to the duration of conventional mechanical ventilation prior to transition to HFOV.

## Discussion

This retrospective study of pediatric patients with acute hypoxic respiratory failure represents the first look at the effect of the duration of conventional mechanical ventilation prior to initiation of HFOV in this patient population. This report of statistically significant differences in mortality based on the duration of lung protective conventional mechanical ventilation prior to HFOV may raise questions as to the benefits of these protective approaches or support a discussion of the benefits of HFOV in protecting 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 proliferation to fibrotic stages reflect a cascade of events that build on each other. 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 pressure, 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. Hotchkiss et al. have suggested that it is not only the amplitude of the pressure swing, but the frequency of swings that may be responsible for the increase in capillary fractures (16). This is also supported by the work by Jackson in ringtail monkeys where he significant reductions in alveolar protein volume when HFOV (12 per cent) was compared to CMV (27 per cent) (17).

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

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, Imai and Sigiura (20—22) when compared with HFOV and more recently by Rotta (23). Several mediators (IL-1 and IL-8) are responsible for the attraction of collagen forming cells to the lung and results in fibrotic lesions. In the baboon model of prematurity Coalson et al. have demonstrated a 40 per cent reduction in lung tissue volume of conventionally ventilated premature baboons as compared to HFOV treated animals (24). In the premature human trials (5, 6) statistically significant reductions in chronic lung were reported as well as in the pediatric randomized controlled trial of HFOV in pediatric ARDS (10).

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

Use of HFOV as the theoretically optimal lung protective strategy, providing the 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.

Conventional ventilation based lung protective strategies may not be as protective as is HFOV. As long as bulk flow tidal volumes are required to remove carbon dioxide, the pressure and volume swings with conventional ventilation will be higher than on HFOV. Additionally, at the same mean airway pressure, the lowest pressure that holds the alveoli open will be higher with HFOV so that there is likely less derecriutment than that reported with low stretch techniques with conventional ventilators (26—28). Nakagawa 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 have found by early use of HFOV.

## Summary

The lenght of conventional mechanical ventilation before HFOV has substantial influence on HFOV efficacy and patient survival in children with severe acute hypoxemic respiratory failure. This report is one more argument to suggest that salvage use of HFOV is of less benefit to pediatric patients with hypoxic respiratory failure. Use of this therapy should be considered early in the course of treatment of any pediatric patient meeting this definition. A randomized controlled trial of early use of HFOV versus conventional ventilation may answer this question more definitively.*

## References

**1. Amato MB, Barbas CS, Medeiros DM et al:** Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. New Engl J Med 1998; 338: 347—354.

**2. Stewart TE, Meade MO, Cook DJ et al:** Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. New Engl J Med 1998; 338: 355—361.

**3. Brochard L, Roudot-Thoraval F, Rouplie E:** Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume reduction in ARDS. Amer J Resp Crit Care Med 1998; 158 (6): 1831—1838.

**4. Brower R et al** (NIH ARDS Network): Prospective, randomized, multicenter trial of 12 ml/kg vs. 6 ml/kg tidal volume positive pressure ventilation for treatment of acute lung injury and acute respiratory distress syndrome (ARMA). Presentation to Amer. Thoracic Soc., San Diego April 1999.

**5. Clark RH, Gerstmann DR, Null DM, deLemos RA:** Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory disetress syndrome. Pediatrics 1992; 89 (1): 5—12.

**6. Gerstmann D et al:** The Provo multicenter early high frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996; 98: 1044—1057.

**7. HiFO Study Group:** Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. J Pediat 1993; 122 (4): 609—619.

**8. Ramanathan R, Ruiz I, Tantivit P, Cayabyab R, deLemos R:**High frequency oscillatory ventilation compared to cenoventional mechanical

*We gratefully acknowledge Reese H. Clark, MD, Director of Research, Pediatrix Medical Group, Inc., Fort Lauderdale, FL for his suggestions and critique of the study.

ventilation in preterm infants with respiratory distress syndrome. Pediat Res 1995; 37: 347A.

**9. Clark RH, Yoder BA, Sell MS:** Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediat 1994; 124 (3): 447—454.

**10. Arnold JH et al:** Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med 1994; 22: 1530—1539.

**11. Beaufils F, Mercier JC, Farnoux C, Saizou C, Thebaud B:** Acute respiratory distress syndrome in children. Curr Opin Pediat 1997; 9 (3): 207—212.

**12. Harel Y, Niranjan V, Evans BJ:** The current practice patterns of mechanical ventilation for respiratory failure in pediatric patients. Heart Lung 1998; 27: 238—244.

**13. Fort P, Farmer C, Westerman J et al:** High-frequency oscillatory ventilation for adult respiratory distress syndrome — a pilot study. Crit Care Med 1997; 25 (6): 937—947.

**14. Bernard GR, Artigas A, Brigham KL et al:** American-European consensus conference on ARDS: definitons, mechanisms, relevant outcomes, and clinical trial coordination. Amer J Resp Crit Care Med 1994; 149: 818—828.

**15. Slutsky AS et al:** ACCP Consensus Conference: mechanical ventilation. Intens Care Med 1994; 20: 64—79.

**16. Hotchkiss J et al:** Increased respiratory frequency worsens ventilator induced lung injury in isolated perfused rabbit lungs. Intens Care Med 1998; A403.

**17. Jackson C et al:** Reduction in lung injury after combined surfactant and high frequency ventilation. Amer J Resp Crit Care Med 1994; 150: 534—539.

**18. Kerr CL et al:** Effects of high frequency oscillation on alveolar surfactant aggregates in acute lung injury. Amer J Resp Crit Care Med 1998; A108.

**19. Froese AB et al:** Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. Amer Rev Resp Dis 1993; 148: 569—577.

**20. Takata M et al:** Intraalveolar expression of tumor necrosis factor gene during conventional and high frequency ventilation. Amer J Resp Crit Care Med 1997; 156: 272—279.

**21. Imai Y et al:** Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation. Amer J Resp Crit Care Med 1994; 150: 1550—1554.

**22. Sigiura M et al:** Ventilator pattern influences neutrophil influx and activation in atelectasis prone rabbit lung. J Appl Physiol 1994; 77: 1355—1365.

**23. Gunnarsson B, Rotta AT, Hernan LJ et al:**Ventilation strategy affects neutrophil elastase activity in bronchoalveolar lavage (BAL) fluid. Pediat Res 1999; A230.

**24. Coalson JJ, Winter V, deLemos RA:** Decreased alveolarization in baboon survivors with bronchopulmonary dysplasia. J Resp Crit Care Med 1995; 152 (2): 640—646.

**25. Slutsky AS:** Multiple system organ failure. Is mechanical ventilation a contributing factor. Amer J Resp Crit Care Med 1998; 157: 1721—1725.

**26. Meyer EC et al:** PEEP at Pflex cannot guarantee a fully open lung after a high pressure recruiting maneuver in ARDS patients. Amer J Resp Crit Care Med 1998; A694.

**27. Richard JC et al:** Influence of tidal ventilation on the pressure-volume curve and the amount of recruitmen. Amer J Resp Crit Care Med 1998; A694.

**28. Nakagawa S et al:** End-expiratory lung volume is determined not only by PEEP but by peak inspiratory pressure in and acute lung injury model. Amer J Resp Crit Care Med 1998; A693.

Received October 15, 1999.
Accepted December 17, 1999.