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Original

High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: A randomized controlled study

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SUMMARY: El-Nawawy A, Moustafa A, Heshmat H, Abouahmed A. High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: A randomized controlled study. Turk J Pediatr 2017; 59: 130-143.

The aim of this prospective randomized study is to compare the outcomes of the early use of either high frequency oscillation (HFO) or conventional mechanical ventilation (CMV) in patients with pediatric acute respiratory distress syndrome (PARDS). We allocated two hundred PARDS patients over 5 years in 1:1 ratio to either mode. The HFO group showed a significantly higher median partial arterial oxygen pressure to fraction of inspired oxygen (PaO_2/FiO_2) values after 24 hours of enrollment (p=0.011), higher oxygenation index (OI) decrease percent (p=0.004) and lower cross-over rates (p<0.001), whereas no differences in 30-day mortality, length of stay (LOS) or ventilation days (p=0.77, p=0.28, p=0.65 respectively). The second day values (after 24 hours) of both OI and PaO_2/FiO_2 were found to be more significant discriminators for mortality when compared to the baseline values (cutoff values >8.5, ≤139 respectively). PARDS patients with baseline OI> 16 had a better chance of survival if initially ventilated with the HFO (*p*=0.004). Although the HFO mode appeared to be a safe mode with a significant better oxygenation improvement (after the first 24 hours) and fewer cross-over rates, it failed to show differences as regards mortality or LOS when compared to the CMV adopting protective lung strategy. In PARDS, HFO had a superior advantage in improving oxygenation, yet with no significant mortality improvement, as multi-organ dysfunction syndrome (MODS) was the most common cause of death in our study and not refractory hypoxemia which is the main problem in PARDS; highlighting that mortality in PARDS is multi-factorial and may not depend only on how fast oxygenation improves.

Key words: conventional mechanical ventilation, randomized, high frequency oscillation, pediatric acute respiratory distress syndrome, outcome.

Acute respiratory distress syndrome (ARDS) is a clinical and physiopathological disorder characterized by acute and diffuse injury to the endothelial and epithelial surfaces of the lung causing a breakdown of gas exchange functions of the lung, resulting in proteinaceous alveolar edema and hypoxemic respiratory failure [1, 2].

In 1994, a definition was recommended by the American–European Consensus Conference Committee (AECC) [3]. In 2012 the Berlin definition was developed as it showed a better predictive validity for mortality[4]. However, in 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) proposed a pediatric-specific definition for acute respiratory distress syndrome which builds on the adult-based Berlin Definition, but has been modified to account for differences between adults and children with acute respiratory distress syndrome, suggesting using this definition for future investigations and clinical care of children with pediatric acute respiratory distress syndrome[5].

ARDS prevalence varies worldwide, the population-based studies in the United States and Europe, published in 1997 and 2008,

indicated that the prevalence of ARDS in adults ranged from 17.9 to 81 per 100,000 person years[6-8]. Reasons for that large variation may include major differences in demographics and healthcare delivery systems[9]. In pediatrics, the prevalence of ARDS is 2–12.8 per 100,000 person years[10-12].

Studies suggested that the overall mortality of ARDS in adults ranges between 27–50% [6, 7, 13, 14].

Published ARDS attributable mortality in children is lower than in adults (18–27%); however, Australian data suggested that PARDS attributable mortality may be similar to adults (35%)[12, 15-18].

Mechanical ventilation is the cornerstone in improving oxygenation [19] but on the other hand, it might also perpetuate lung injury by over-distending and rupturing healthy alveoli and by triggering a secondary inflammatory response that intensifies lung injury from repeatedly opening and collapsing lung units.[20-23]

Lung protective ventilation strategy targets limiting alveolar distension, recruiting non-aerated alveoli, and preventing further alveolar collapse. Conventional mechanical ventilation using low tidal volume combined with adequate positive end expiratory pressure (PEEP) has been shown to reduce mortality[24, 25].

High frequency oscillation appeared as an alternative technique of ventilation in which extremely small tidal volumes (1-3 ml/kg) are delivered at high frequencies (3-15 Hz) with an oscillatory pump and constant lung recruitment[26], hence it meets theoretically the goals of a strategy of lung protective ventilation[27].

Some centers use high frequency oscillation in patients with ARDS who do not tolerate conventional mechanical ventilation[28-30], but its use other than as a "rescue" treatment remains controversial[31, 32].

In a recent systematic review included 10 randomized controlled trials studying the use of HFO versus CMV in moderate and severe ARDS in adult patients, there was no significant difference in hospital or 30-day mortality between both groups[33].

Researches on pediatric population appear to be insufficient and inconclusive. It is our rationale to study the clinical benefits of HFO compared to CMV in PARDS patients.

In this prospective study, we aimed to compare between the use of HFO and CMV in moderate and severe PARDS patients as defined by AECC as regards oxygenation improvement, mortality, air leaks, ventilation days, length of stay and free mechanical ventilation days.

Material and Methods

Study design

This randomized controlled study was performed in a 9 bedded pediatric intensive care unit (PICU) located in a teaching tertiary care pediatric hospital. We compared the use of HFO versus CMV in PARDS patients as initial modes of ventilation[3] over 5 years (from January 2011 to April 2016). For HFO we used the Fabian High-Frequency Oscillatory Ventilator (Switzerland - Accutronic) ® and for CMV we used the Avea (USA- CareFusion) ® and SERVO-i (Sweden- Maquet) ® ventilators. The Fabian ventilator is fully functional as HFO mode for neonates through pediatrics weighing 30 kilograms. An informed consent was obtained from patients' parents/ legal guardians prior to study entry. This study was approved by the University Ethical Committee (serial number 020687).

The study design was aimed to be parallel. Block randomization was done using Web-based software to assign 200 patients to either HFO or CMV in a 1:1 ratio and sequentially numbered sealed closed envelopes were used by physicians to allocate each patient to either group.

Patients

Two hundred PARDS patients who were undergoing mechanical ventilation were included in the study if they had $PaO_2/FiO_2 \leq$ 200 mm Hg or less and bilateral pulmonary infiltrates were visible on chest radiography without evidence of left atrial hypertension, according to AECC definition of ARDS[3] at the start of the study, as the Berlin definition was published at 2012 after the onset of the study[4]. By reviewing the Berlin definition after it first appeared, we found that all of our cases were considered included in the moderate and

severe categories of ARDS, and this was our determination throughout our study.

Exclusion criteria were: (1) patients weighing more than 30 kilograms (2) pulmonary edema of cardiac origin or due to volume overload, (3) patients with congenital heart disease, (4) diagnosis of cardiomyopathy or myocarditis, (5) post cardiac surgery for congenital heart defects. Data on demographics, patient diagnosis, mechanical ventilation data, severity of illness, and outcomes were collected. Specific data collected for demographics and severity of illness included age, sex, provisional diagnosis, Pediatric Index of Mortality 2 (PIM2) score, PICU length of stay, mechanical ventilation (MV) days and MV free days.

ARDS was categorized into primary and secondary. Primary causes included pneumonia, aspiration (gastric contents/ barium/ gastrografin), and kerosene toxicity. Secondary causes included severe sepsis and septic shock.

Ventilator protocols

All patients included in our study were allocated to either to HFO group or CMV group once the inclusion criteria were met.

Table I. Comparison Between the Two Treatment Groups.

	Ventilator groups		
	CMV (n =100)	HFO (n =100)	p value
Male sex, n (%)	66 (66.0)	52 (52.0)	0.044
Age (months)	7.75 (3.0 – 17.75)	7.0 (5.0 – 12.0)	0.896
Height (cm)	69.0 (59.0 – 79.75)	67.5 (61.25 – 76.0)	0.596
Weight (kg)	7.8 (5.0 – 11.65)	8.0 (5.33 – 8.9)	0.658
Diagnosis on admission			
Sepsis, n (%)	43 (43.0)	54 (54.0)	0.120
Respiratory, n (%)	57 (57.0)	46 (46.0)	
PIM 2 score	56.55 ± 18.36	55.80 ± 19.02	0.778
Baseline OI	13.0 (10.0 – 18.3)	16.0 (11.78 – 22.7)	0.005
OI after 24 hours	8.2 (6.58 – 14.65)	7.9 (6.5 – 14.0)	0.940
p_0	<0.001	<0.001	
OI decrease percent	27.4 (20.89 – 43.5)	41.9 (24.86 – 52.5)	0.004
Baseline PaO_2/FiO_2 –mm Hg	110.0 (92.3–143.0)	110.0 (87.3–141.0)	0.818
PaO_2/FiO_2 after 24 hours –mm Hg	174.0(120.3–200.0)	191.0 (138.5– 241.0)	0.011
p_0	<0.001	<0.001	
PaO_2/FiO_2 increase percent	37.5 (26.62 – 72.03)	67.5 (27.16– 109.04)	0.004
Baseline MAP cm H_2O	14.5 (13.0 – 18.0)	18.5 (15.0 – 20.0)	<0.001
MABP (mm Hg) (after 24 hours)	59.8 ± 9.8	57.2 ± 10.2	0.07
Baseline PCO_2	52.4±13.5	58.2±10.6	0.013
PCO_2 after 24 hours	52.8± 10.6	54.1 ± 11.4	0.42
Nonsurvivors, n (%)	43 (43.0)	45 (45.0)	0.776
Cross over, n (%)	16 (16.0)	0 (0.0)	<0.001
Air leak, n (%)	11 (11.0)	8 (8.0)	0.631
30 days mortality, n (%)	43 (43.0)	45 (45.0)	0.776
Midazolam (micg/kg/min)	2.69 ± 0.98	4.85 ± 1.05	<0.001
Atracurium intake, n (%)	10 (10.0%)	85 (85.0%)	<0.001
Atracurium (mg/kg/hr)	0.625 (0.600-0.725)	0.800 (0.700-0.975)	0.003

Normally quantitative data was expressed in mean ± SD and was compared using Student t-test. Abnormally quantitative data expressed in median and interquartile range (IQR) and was compared using Mann Whitney test. p0: p value for Wilcoxon signed ranks test for comparing between baseline and after 24 hours. MABP = mean arterial blood pressure. OI: oxygenation index

Table II. Causes of Death Among Both Studied Groups.

	Ventilator mode mortalities		p value
	CMV (n =43/100)	HFO (n =45/100)	
Probable causes of death			
MODS, n (%)	35 (81.4)	37 (82.2)	0.160
Renal failure on dialysis, n (%)	4 (9.3)	1 (2.2)	
Refractory hypoxemia, n (%)	1 (2.3)	5 (11.1)	
Massive pulmonary hemorrhage, n (%)	3 (7.0)	1 (2.2)	
Cardiogenic shock, n (%)	0 (0.0)	1 (2.2)	

MODS: multiple organ dysfunction syndrome

HFO protocol

HFO randomized patients were started HFO treatment once the diagnostic criteria were met, as early HFO comparative use was the main aim of the present study. MAP initially was set 3-5 cmH_2O above the mean airway pressure on conventional mechanical ventilation as a starting point, and it was allowed to be increased gradually in a stepwise approach as long as oxygenation improves while FiO_2 is fixed, till the point oxygenation stops to improve. HFO patients who did not show adequate oxygenation improvement were subjected to lung recruitment maneuver (LRM), by applying a constant mean airway pressure (MAP) for a specific time interval (sustained inflation), starting with MAP of 20 cmH_2O for 20 seconds, and increasing MAP in a stepwise approach (if oxygenation did not improve) to 30 cmH_2O for 30 seconds, and to 40 cmH_2O for 40 seconds according to the clinical situation. Recruitment maneuvers were allowed to be repeated as needed. Optimum lung volumes were defined by chest X-ray if expansion reached 8-9 ribs posteriorly. Initial frequencies were set between 5-12 Hz. I:E ratio was set 1:1 and changed to 1:2 if hyperinflation appeared or to manage hypercarbia. Amplitudes were set to assure tidal volumes 1.5-3 ml/ kg either directly, or by using the volume guarantee option in the HFO device mode, assuring adequate chest wiggling. In Fabian device, bias flow could be set from a range of 5-20 L/min in a 1 lit increment. In our PICU, initial flow was chosen from 8-18 L/min according to weight (wt < 6 kg= 8-12 Lit), (6-15 kg =12-15L), (≥15 kg= ≥15 L). The main targets were to maintain a stable mean airway pressure in face of spontaneous breaths, if any, and to prevent re-breathing as a cause of hypercarbia through adequate flows in the circuits. The lowest acceptable value was chosen, as if it is inappropriately increased, may increase resistance and increase infants work of breathing. HFO patients were assured for adequate sedation using sedatives (Midazolam with/without Fentanyl or Ketamine), while neuromuscular blocker (Atracurium) was used during LRM and in patients with high flow demands spontaneous breaths. Adequate humidification for the circuits was assured for every case, and closed suctioning technique was used.

Weaning phase

During weaning among cases showed improvement, our primary target was to lower FiO_2 to <0.60 with a target oxygen saturation >90% while achieving optimum lung volumes through keeping mean airway pressure constant, after that, MAP and FiO_2 were allowed to be reduced simultaneously. MAP was reduced in small increments of 1-2 cmH_2O every 4-6 hours as long oxygenation was maintained, otherwise if adequate oxygenation started to be lost, MAP was restored back to the previous setting. However, in cases of hyper inflated lungs, MAP was immediately decreased in more increments of 3-5 cmH_2O followed by immediate Chest X-ray to optimize the MAP. Amplitudes were allowed to be lowered if an increase in delivered tidal volumes was observed or when there was excess CO2 wash. When oxygenation was maintained above 95% with MAP of 12-15 cmH_2O and FiO_2=0.4 for 6 hours, preparation to transition to CMV was done through assuring adequate spontaneous breathing after stoppage of neuromuscular

blockers and titrating sedation.

Oscillatory rates were between 6-10 Hz and oscillatory pressure amplitudes were set to target no more than 3 ml/kg tidal volume as measured by the calibrated wye piece hotwired flow sensor, while assuring adequate chest wall wiggling. Pressure amplitudes were chosen to assure adequate blood gases PCO_2. Hypercarbia was permissible as long as arterial pH was ≥7.2 with HCO_3 ≥ 19mmHg. Patient monitoring was through PCO_2 for adjusting pressure amplitudes and tidal volumes and through serial chest X-rays, PaO_2 and oxygen saturation for assessing lung volumes and adjusting MAP.

CMV protocol

Protective lung strategy was accomplished by choosing driving pressures to deliver 5-8 ml/kg tidal volumes. Hypercarbia was permissible as long as arterial pH was ≥7.2 and HCO_3 ≥ 19 mmHg.

CMV patients who needed lung recruitment were subjected to LRM through gradually increasing PEEP to 15-20 cmH_2O and driving pressure 15 -20 cmH_2O keeping the peak airway pressure no more than 35 cmH_2O, for 1-2 minutes followed by decremental PEEP titration every 1-2 minutes till achieved best oxygenation and/or best respiratory system compliance values. Inspiratory time to expiratory time (I: E) ratio was set to 1:1 during recruitment maneuver. Inverted I: E ratio ventilation mode was used as indicated by clinical condition.

During any recruitment maneuver, all vital signs were closely monitored, and if any signs of hypotension, bradycardia, desaturation or air leak appeared, recruitment maneuver would have been immediately stopped.

The oxygenation goal was to maintain an O_2 saturation >90% with a FiO_2≤ 0.6while achieving optimum lung volumes through keeping mean airway pressure constant, after which MAP and FiO_2 were allowed to be reduced simultaneously. Driving pressures were weaned as respiratory system compliance

Table III. Survivors and Non-survivors Groups' Comparison.

	Mortality		
	Survivors (n =112)	Nonsurvivors (n =88)	p
Male sex, n (%)	64 (57.1)	54 (61.4)	0.547
Age (months)	7.0 (5.0 – 15.0)	7.0 (4.0 – 14.0)	0.773
Height (cm)	68.5 (59.0 – 76.0)	67.5 (61.0 – 80.0)	0.639
Weight (kg)	7.8 (5.0 – 8.8)	8.0 (5.3 – 9.0)	0.483
PIM 2 score	47.24 ± 15.56	67.54 ± 15.92	<0.001
Baseline OI	12.6 (10.0 – 18.03)	18.2 (12.0 – 28.35)	<0.001
OI after 24 hours	6.8 (6.1 – 8.48)	14.0 (12.0 – 28.35)	<0.001
p_0	<0.001	0.007	
OI decrease percent	41.19 (26.4 – 54.54)	27.1 (-18.77 – 44.46)	<0.001
Primary ARDS (total n=103)	56 (54.4)	47 (45.6)	0.63
Secondary ARDS (total n=97)	56 (57.7)	41 (42.3)	
Air leaks	3 (2.7)	16 (18.2)	<0.001
Baseline PaO_2/FiO_2 –mmHg	120.5 (93.0 – 145.0)	98.0 (79.25 – 130.0)	0.002
PaO_2/FiO_2 after 24 hours –mmHg	169.5 (175.0–227.75)	122.0 (76.0 – 190.0)	<0.001
p_0	<0.001	<0.001	

Normally quantitative data was expressed in mean ± SD and was compared using Student t-test. Abnormally quantitative data expressed in median and interquartile range (IQR) and was compared using Mann Whitney test.
p_0: p value for Wilcoxon signed ranks test for comparing between 1st hour and after 24 hours.
OI: oxygenation index

improved and an increase in delivered tidal volumes was observed. The ventilatory goal was to establish an arterial pH≥7.20 with HCO_3 ≥19 mmol/L while minimizing peak inspiratory pressures. Minimal effective targeted sedation (benzodiazepines alone or with fentanyl) was used to facilitate synchronization. A neuromuscular blocker (atracurium) was used only during lung recruitment and if sedation alone was ineffective in achieving synchronous ventilation.

Patients monitoring was through PCO_2 for adjusting driving pressures and tidal volumes and through serial chest X-rays, PaO_2 and oxygen saturation for assessing lung volumes and adjusting PEEP.

Cross over

Patients were crossed over from HFO to CMV in the following conditions: a) hypotension not responding to inotropes; b) intractable hypercarbia occurred with pH <7.2 and HCO_3 ≥ 19mmol/L, despite choosing maximal safe pressure amplitudes and minimal frequencies.

Patients were crossed over from CMV to HFO in the following conditions: a) persistent air leaks or those necessitating more than one chest tube; b) failure of oxygen saturation to reach 90% despite good lung volumes even while using ARPV mode with inverted I:E ratio and a PEEP of 12-14 and PIP 30- 35 cmH2O; c) intractable hypercarbia with pH < 7.2 with HCO_3> 19 mmol/L, using maximal tidal volumes of 7 ml/kg.

Extubation

Extubation readiness was assessed daily and requires the following: (1) PaO_2/FiO_2 ≥ 200; (2) PEEP ≤ 5 cm H_2O; (3) Adequate cough during suction (intact airway reflexes). Extubation was considered when the patient's condition had been stable for 12 to 24 h while adequate oxygenation could be maintained with a FiO_2 of 0.4 and a MAP ≤8 cm H_2O.

Non-pulmonary treatments for both groups

Parenteral nutrition was started from admission for all patients, targeting 70-75% of mean caloric intake, and trophic feeds were started as soon as shock was resolved or when the general condition becomes stable for 24-48 hours. Net fluid balance was done daily for every case aiming to prevent positive fluid balance while maintaining optimum intravascular volume and accepted urine output.

Table IV. Comparison Between Survivors in the Two Studied Groups.

	Ventilator group survivors		p
	CMV (n = 57)	HFO (n = 55)	
PIM 2 score %	47.85 ± 17.48	46.62 ± 13.41	0.677
Baseline OI	11.8 (9.0 – 13.9)	16.0 (11.2 – 22.0)	0.001
OI after 24 hours	6.8 (6.1 – 8.4)	7.5 (6.0 – 8.5)	0.594
OI decrease percent	32.2 (24.44 – 42.37)	50.0 (40.63 – 57.85)	<0.001
Baseline PaO_2/FiO_2–mmHg	116.0 (98.0 – 145.0)	121.0 (91.0 – 140.0)	0.302
PaO_2/FiO_2 after 24 hours –mmHg	191.0 (161.0 – 210.0)	221.0 (191.0– 246.0)	<0.001
PaO_2/FiO_2 increase percent	37.9 (34.41 – 72.73)	91.36 (65.0 – 113.3)	<0.001
PICU LOS days	8.0 (6.0 – 10.0)	8.0 (6.0 – 18.0)	0.282
Days of MV	5.0 (4.0 – 7.0)	5.0 (4.0 – 7.0)	0.658
MV free days till 30 days	25.0 (23.0 – 26.0)	25.0 (23.0 – 26.0)	0.658
Midazolam (micg/kg/min)	2.7 ± 0.92	5.2 ± 0.77	<0.001
Atracurium intake, n (%)	3(5.2)	52 (94.5)	<0.001

Normally quantitative data was expressed in mean ± SD and was compared using Student t-test. Abnormally quantitative data expressed in median (IQR) and was compared using Mann Whitney.
LOS: length of stay; MV: mechanical ventilation; OI: oxygenation index

Outcomes

Evaluated outcomes included: comparing oxygenation improvement by measuring the baseline (after first hour of enrollment) and 2nd day (after 24 hours) values of both $PaO_2/FiO_2$and OI, 30-day mortality, air leaks occurrences and cross over rates. Among survivors: length of stay, ventilation days, MV free days till 30-day and PICU ventilator free days were compared.

This research is registered in the Cochrane library retrospectively by PACTR201609001779105.

Statistical analysis

All analyses were conducted on an intention to-treat basis. Sample size was estimated based on data from a previous randomized trial[34]. We calculated that a minimum required sample sizes of 36 patients for each group (total 72) will achieve 86% power to detect a difference of 7 between the null hypothesis considering that both groups mean oxygenation index is 18 and the alternative hypothesis that the mean oxygenation index of group receiving HFO is 25.2 compared to mean oxygenation index of 18 in the group receiving CMV with estimated group standard deviations of 13 and 7.4 respectively and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test. Sample size was calculated using NCSS PASS 2004 program.

We compared changes in baseline PaO_2/FiO_2 and OI values in the same group and their values after 24 hours using Wilcoxon signed ranks test. Kolmogorov-Smirnov test was used for testing normality. Student's t-test was used to compare normally distributed quantitative data and was represented with mean and standard deviation (SD), while non-normally distributed quantitative data were analyzed with Mann-Whitney test and were represented with median and interquartile range (IQR). Chi-square test was used to compare 30-day mortality and air leaks between both groups.

The level of significance we adopted was $p < 0.05$. Calculations were performed by the IBM SPSS program version 20.0. Post-hoc achieved power analysis was calculated using GPower version 3.1.9.2, and it was done on 2 steps; the first analyzed the sum of both groups (200 patients) and showed a power of 1, the second step analyzed each treatment group separately and showed a power of 0.99 for each of CMV and HFO groups.

Results

Comparison between the baseline data and outcomes of both groups

Both groups were comparable for age, height, weight and PIM 2 scores (Table I). The baseline median OI in HFO group was significantly higher in the HFO group compared to the CMV group (16 (IQR 11.7-22.7), 13 (IQR 10-18) respectively, $p=0.005$). In the CMV group 16% crossed over to HFO, while no HFO allocated cases crossed over to CMV ($p<0.001$). The baseline median MAP was significantly higher in the HFO group than the CMV group (18.5 (IQR15-20), 14.5 (IQR 13-18) respectively, $p<0.001$). The HFO group

Table V. Receiver Operating Characteristic Curve Sensitivity and Specificity of Baseline and After 24 Hours Oxygenation Parameters (OI and PaO_2/FiO_2).

	Cutoff	AUROC	P	Sensitivity	Specificity	PPV	NPV	95% CI LL	95% CI UL
Baseline OI	>16.6	0.681	<0.001	55.68	75.0	63.6	68.3	0.607	0.756
OI after 24 hrs	>8.5	0.797	<0.001	72.73	78.57	72.7	78.6	0.730	0.864
Baseline PaO2/FiO_2	≤114	0.625	0.002	67.05	58.93	56.2	69.5	0.544	0.706
PaO_2/FiO_2 after 24 hours	≤139	0.766	<0.001	55.68	91.96	84.5	72.5	0.694	0.838

AUROC: area under the receiver operating characteristic curve; CI: confidence interval; LL: lower limit; NPV: negative predictive value; OI: oxygenation index; PPV: positive predictive value; UL: upper limit

Table VI. Baseline OI in Survivors in Both Groups.

	Survivors (n =112)	
	CMV (n=57)	HFO (n=55)
Baseline OI, n (%)		
4 – 8	3 (5.3)	0 (0.05)
>8 – 16	45 (78.95)	33 (60.05)
>16	9 (15.85)	22 (40.0)
p	^{MC}p=0.004	

MC: Monte Carlo for Chi square test

showed a higher baseline PCO_2 (p= 0.013), but both groups did not show differences regarding 24 hours values of mean arterial blood pressure or 24 hours values of PCO_2 (p=0.07, 0.42, respectively). Midazolam mean dosages (mic/kg/min) were significantly higher in the HFO group (p<0.001). Significantly higher percent of patients among the HFO group received daily Atracurium intake, with significantly higher dosages (p<0.001, p= 0.003 respectively). HFO initial parameters are described in Table VII.

Outcomes

30-day mortality

It did not differ between the CMV and the HFO groups (43% and 45% respectively, p= 0.776). Kaplan-Meier survival curves did not show significant differences between both groups (p= 0.787; Fig.1).

Air leaks

Air leak syndromes incidence did not differ significantly between both groups (p= 0.631).

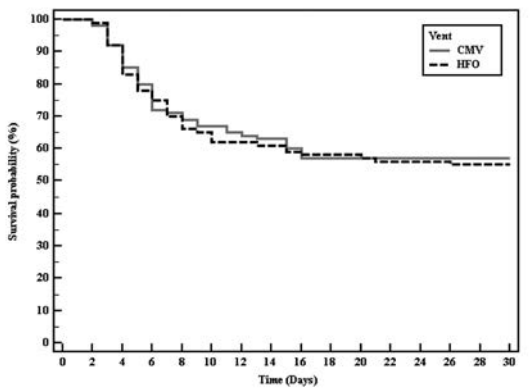

Fig. 1. Kaplan-Meier survival curve for both treatment groups for the first 30 days (p=0.787)

Oxygenation improvement

PaO_2/FiO_2 ratio

Both groups showed comparable PaO_2/FIO_2 on enrollment, but the HFO group showed a significantly higher median PaO_2/FiO_2 than the CMV group after 24 hours of enrollment (191,174, respectively, p= 0.011). The median value of PaO_2/FiO_2 increase percent, calculated as (PaO_2/FiO_2after 24 hours –PaO_2/FiO_2

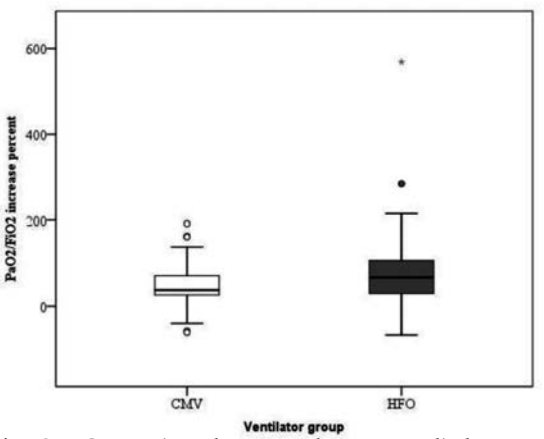

Fig. 2a. Comparison between the two studied groups according to PaO2/FiO2 increase percent (p=0.004*).

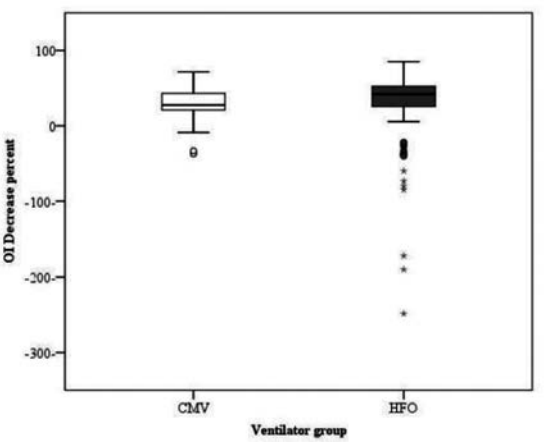

Fig. 2b. Comparison between the two studied groups according to OI decrease percent (p=0.004*)

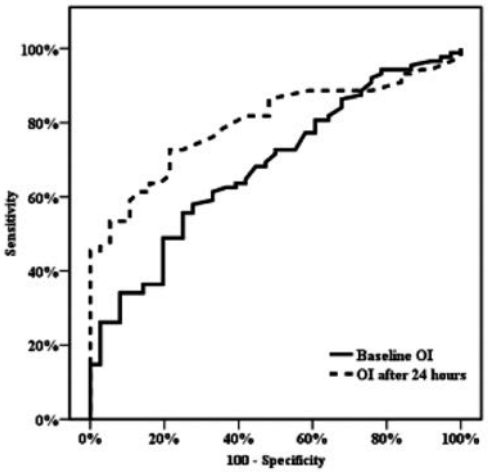

Fig. 3. Receiver operating characteristic (ROC) curves for OI (baseline and after 24 hours).

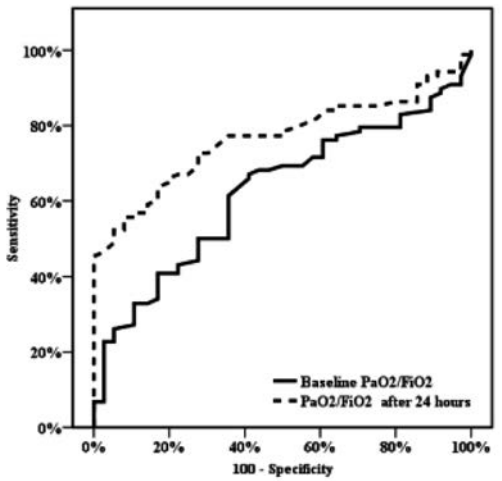

Fig. 4. Receiver operating characteristic (ROC) curves for PaO2/FiO2 (baseline and after 24hours)

baseline)*100/ PaO_2/FiO_2 baseline, was significantly higher among HFO group (67.47%, 37.5%, respectively, p= 0.004; Fig. 2a).

Oxygenation index

Although the median OI after 24 hours of enrollment was lower in the HFO group, it did not reach a statistical difference (p =0.94), but the median OI decrease percent, calculated as (baseline OI- OI after 24 hours)*100/ baseline OI), was significantly higher among the HFO group (41.9%, 27.4%, respectively, p= 0.004; Fig.2b) as the baseline median OI was significantly higher among the HFO group (p=0.005).

Causes of death

MODS was the most common cause of death (81.8% of all deaths), while refractory hypoxemia was the cause in only 6.8% of deaths (Table II). In kidney failure group, we specified cases with acute renal injury who needed peritoneal dialysis and death was their fate.

Comparison between survivors and non-survivors groups

Non-survivors showed significantly higher values of PIM 2 score on admission, baseline OI, OI after 24 hours and air leaks versus survivors (p<0.001, p<0.001, p<0.001, p<0.001 respectively), while survivors showed higher OI decrease percent, baseline PaO_2/FiO_2, PaO_2/FiO_2after 24 hours and PaO_2/FiO_2 increase percent (p<0.001, p=0.002, p<0.001, p<0.001 respectively) (Table III). Air leak syndromes showed non adjusted odds ratio (OR) for mortality of 8.074 (95% CI 2.27-28.7). There was no significant difference in mortality regarding ARDS category whether primary or secondary (p=0.63).

Outcomes among survivors of both groups

Oxygenation improvement

Results showed a comparable PIM 2 score and baseline PaO_2/FiO_2 (p=0.67, p=0.3 respectively). While OI after 24 hours did not differ significantly between both groups, the baseline OI among the HFO group was significantly higher and OI decrease percent was higher among HFO group (p=0.59, p= 0.001, p<0.001 respectively). Also the HFO group showed higher median PaO_2/FiO_2 after 24 hours and higher median PaO_2/FiO_2 increase

Table VII. Baseline HFO Parameters.

Parameters	Mean ± SD
FiO_2	0.76 ± 0.09
Amplitude (cm H_2O)	48.9 ± 9.6
Frequency (Hz)	7.8 ± 1.33
Baseline MAP (cm H_2O)	18.65 ± 4.14

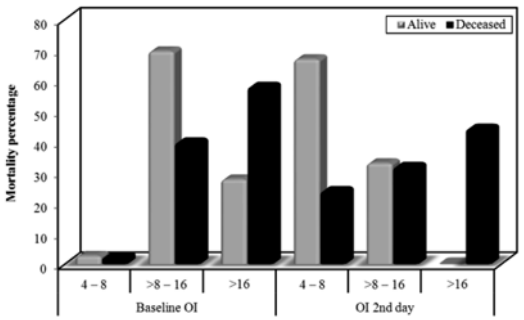

Fig. 5. Relation between mortality and OI grades (baseline OI and OI after 24 hours; p <0.001, p<0.001 respectively).

percent ($p<0.001$, $p<0.001$ respectively) (Table IV).

Length of stay and ventilation days

Both the CMV and HFO groups did not show statistical differences as regards PICU length of stay ($p=0.28$), mechanical ventilation (MV) days ($p=0.65$), MV free days till 30 days ($p=0.65$) and MV free days in PICU ($p=0.57$) (Table IV).

Midazolam and Atracurium intake

The HFO group had a significantly higher percent of patients received Atracurium and significantly higher Midazolam infusion dosages ($p<0.001$, $p<0.001$ respectively) (Table IV).

Receiver operating characteristic (ROC) curves and mortality discrimination

The baseline OI and OI after 24 hours were statistically significant discriminators of occurrence of mortality with areas under the receiver operating characteristic (AUROC) curve = 0.68 and 0.79 respectively (Fig. 3, Table V). Pair wise comparison showed that the OI after 24 hours was more significant discriminator for mortality than baseline OI ($p<0.001$; cutoff values of >8.5 versus >16.6, respectively).

The baseline PaO_2/FiO_2 and PaO_2/FiO_2 after 24 hours were statistically significant discriminators of occurrence of mortality with AUROC curve = 0.62and 0.76 respectively (Fig. 4, Table V). Pair wise comparison showed that PaO_2/FiO_2after 24 hours was more significant discriminator for mortality when compared to baseline PaO_2/FiO_2 ($p<0.001$; cutoff values of ≤139 versus ≤114, respectively).

Relation between mortality and OI grades

The results showed that the mortality increased as the baseline OI increased (p <0.001) and also as OI after 24 hours increased (p <0.001; Fig. 5).

There was a higher incidence of survivors in the HFO group with baseline OI >16 than the corresponding CMV group (40% versus 15.8%, $p=0.004$) (Table VI).

Discussion

The present study aimed at evaluating early application of HFO compared to CMV on the PARDS patients once the patients met the inclusion criteria. We randomly allocated 200 PARDS patients in 1:1 ratio to HFO and CMV modes. Mortality rates among CMV and HFO didn't show significant differences. Kaplan-Meier survival curve did not show statistical differences. The present results matched previous studies results including one pediatric RCT [35] and some adult studies as well including 2 meta analyses[34, 36-38], while other studies stated improved mortality among HFO group, their results were not statistically significant[36, 39]. In a review by Kneyber et al.[40] in 2012 about published clinical experiences about HFO in pediatrics, it was concluded that a beneficial role of HFO on mortality is not established; yet it proposed a question about the optimum timing and settings of HFO has been employed.

On the other hand, a retrospective observational study concluded that application of early HFO was associated with worse outcomes and higher mortality among pediatrics with acute hypoxemic respiratory failure[41]; however, that study was retrospective lacking randomization and missing data on certain key variables as PaO_2, FiO_2, PaO_2/FiO_2, presence or absence of air leaks and causes of death.

In the present study, MODS was the most common cause of death among both groups (81.4% in CMV, 82.2% in HFO) followed by a small percent with refractory hypoxemia (2.3% in CMV, 11.1% in HFO). Several studies in adults showed similar results; a study by Stapleton et al.[42] (consecutive cohorts analysis) found that MODS was the most common cause of death (30 to 50%), while hypoxemic respiratory failure caused a small percentage (13 to 19%) of deaths. Also, MODS was the most common single cause (50%) in a study

by Bersten et al.[43] A RCT by Derdak et al.[36] stated a similar finding but with incidences of (50% in CMV and 56% in HFO) for MODS as a cause of death[36].

As regards pediatrics, two prospective studies showed that MODS was the most frequent cause of death among ALI/ARDS pediatric patients with an incidence of 51%[11] and 93%[15]. So it appears that MODS is the commonest cause of death and not refractory hypoxemia; which is the main problem in ARDS.

These data may partially explain why mortality rates did not differ significantly in the present study although the apparent advantage of HFO in improving oxygenation over the first 24 hours, as mortality appears to be multi-factorial and may not depend only on how fast oxygenation improves. A research suggests that repetitive overstretching or collapse of lung units with every respiratory cycle can generate local and systemic inflammation, contributing to multi-organ dysfunction and leading to death[44]. This explains the relationship between ventilator induced lung injury (VILI) and initiating or augmenting MODS, hence the importance of preventing VILI in every PARDS case.

As regards oxygenation improvement, we found that HFO significantly improved oxygenation after 24 hours of enrollment, a finding that is comparable with results in several pediatric studies[35, 45-47] and adult studies[34, 36]. Also survivors among HFO group showed significant higher OI decrease percent, PaO_2/FiO_2after 24 hours and higher PaO_2/FiO_2 increase percent.

Although that apparent advantage of HFO in improving oxygenation, survivors of both groups did not show differences in regards to PICU LOS or MV days coinciding with one pediatric RCT[35], one adult RCT[34] and two recent trials in 2013 (OSCAR and OSCILLATE trials)[37, 38] which revealed no statistical differences as regards the total duration of ICU stay or the total hospital stay. Possible explanations in the present study may include; the increased use of neuromuscular blockers (NMBs) in addition to significantly higher doses of sedatives (midazolam) among HFO groups, in addition to the use of CMV mode during weaning from the HFO mode instead of direct extubation to nasal cannulae or mask. Arroliga et al.[48] found NMBs use is associated with longer duration of mechanical ventilation, weaning time, stay in the ICU, and higher mortality. Kress et al.[49] showed in a RCT that continuous sedation had a significantly longer stay in the ICU and a significantly longer duration of mechanical ventilation. As HFO is associated with more usage of NMBs and continuous sedation, we expect that an earlier trial of transition from the HFO mode to the CMV mode as soon as possible as OI improves could be an optimal timing for reduction in NMBs and sedation dosages; hence MV days and total ICU stay may shorten.

The HFO group showed lower air leaks occurrence (8% versus 11%), but without statistical significance. Several studies showed no statistical differences in air leaks frequencies between both modes[34-36, 50]. A meta-analysis[38] showed higher rate of new onset barotraumas among HFO group, but did not reach statistical difference after all. HFO use seems from a theoretical point of view to be the safest ventilatory mode as it delivers tidal volumes no more than the dead space with constant mean airway pressure to prevent atelectasis[51]. On the other hand the CMV protective lung strategy as stated by the Acute Respiratory Distress Syndrome Network[24] limiting tidal volumes and peak pressures with adequate positive end expiratory pressures (PEEP) seems to be working well. In the present study air leaks were significantly higher among nonsurvivors group.

Sixteen cases (16%) of CMV crossed over to HFO treatment after allocation, while no cross over occurred among HFO group. The causes included persistent air leaks (2 cases) and oxygenation failure despite good lung volumes (14 cases), while in an adult RCT by Bollen et al.[34] there was no statistical differences in cross over among both groups.

As regards the survivors and nonsurvivors, there were no differences as regards gender, weight, height or age. PIM 2 scores on admission were significantly higher among nonsurvivors group as well as baseline OI and after 24 hours OI, while the survivors group had significantly higher values of baseline PaO_2/FiO_2, PaO_2/FiO_2 after 24 hours, PaO_2/FiO_2 increase percent and OI decrease percent.

The OI trend was found to predict mortality in several studies[35, 36, 52]. One of them is a

pediatric RCT by Arnold et al.[35] found that OI was significantly lower among survivors during first 72 hours. Other several pediatric investigators have demonstrated stronger associations between OI and mortality for each day the patient remains on mechanical ventilation[53, 54]. Data from two pediatric studies[11, 55] suggested that OI may have better discriminatory value for mortality than PaO_2/FiO_2, and the relationship between OI and mortality strengthens as the patient remains on mechanical ventilation for the first 3 days [55].

So it was recommended that OI, in preference to PaO_2/FiO_2, should be the primary metric of lung disease severity to define PARDS [5].

In the present study, we found a significant increase in mortality rates as the baseline OI and OI after 24 hours increased. Khemani et al.[5] reviewed seven PARDS studies[10, 11, 15, 18, 53, 56, 57] and found stepwise increases in mortality as the OI severity increases between OI groups (4-8 group, 8-16 group and >16 group).

We discriminated mortality using baseline and 2nd day values of OI and PaO_2/FiO_2. The OI after 24 hours and PaO_2/FiO_2after 24 hours were statistically significant discriminators for mortality when compared to baseline OI and baseline PaO_2/FiO_2respectively.Cutoff value for OI after 24 hours was >8.5 and for PaO_2/FiO_2after 24 hours was ≤ 139.In the present study, no case with OI after 24 hours>16 survived.

The present study showed that there was a higher incidence of survivors in HFO group with baseline OI>16 in accordance with observational studies that showed that better survival rates in more severe ARDS with higher OI occurred with HFO treatment[28, 34, 52]. Also, HFO has been recommended for patients who require high mean airway pressure and FiO_2 exceeding 60% corresponding to an OI > 20 when PaO_2=60 mmHg[58].

Although the HFO group showed a significant improved oxygenation when compared to the CMV group after 24 hours of enrollment, there were no significant differences as regards 30-day mortality, LOS or MV days. Mortality appears to be multi-factorial and may not depend only on how fast oxygenation improves. We assume that increased NMBs use and higher sedation dosages among HFO group might have prolonged their LOS and increased their MV days. We propose that an earlier trial of transition from the HFO mode to the CMV mode as soon as OI improves may be an attempt to reduce LOS among HFO treated patients; highlighting that both modes may have a co-operative role rather than a competitive role. This could be a subject for further studies. The HFO mode appears to be a safe mode in PARDS with significantly lower rates of cross-over and with a better chance of survival in patients with baseline OI > 16. The limitation of this study is that it is a single center study and more studies about the hemodynamic parameters during mechanical ventilation are needed.

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