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High frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome – a retrospective study

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Background: At present there are limited data about the effects of high frequency oscillatory ventilation (HFOV) in adult patients with acute respiratory distress syndrome (ARDS). This study evaluates efficacy of HFOV in such patients.
Methods: Sixteen ARDS patients, mean age 38.2 years (range 18–76), that underwent HFOV between 1997 and 2001 were enrolled in the study and evaluated in retrospect. FIo_2, arterial blood gases, mean airway pressure (mean P_{aw}), blood pressure, heart rate and central venous pressure were recorded by 4, 8, 12, 24, 48 and 72 h of HFOV and compared to conventional mechanical ventilation (CMV) at baseline (4 h prior to HFOV).
Results: On admission to the ICU, mean Simplified Acute Physiology score (SAPS II) was 40.3 (SD 12.6). Main causes of ARDS were pneumonia (9/16) and burn injuries (4/16). At baseline the patients had severe ARDS as noted by a mean lung injury score (LIS) of 3.2 (SD 0.3) and Pao_2/FIo_2 ratio 12.2 (SD 3.2) kPa. Within 4 h of HFOV, Pao_2/FIo_2 increased to 17.3 (SD 5.9) kPa ($P = 0.016$). Throughout HFOV, Pao_2/FIo_2 was significantly higher than at baseline. There were no significant changes in haemodynamic parameters. Ending HFOV after 6.6 (SD 3.2) days, survivors ($n = 11$) significantly reduced their Sequential Organ Failure Assessment Score (SOFA) compared to baseline. Survival at 3 months was 68.8%.
Conclusion: HFOV effectively improves oxygenation without haemodynamic compromise. During HFOV, the SOFA score may predict outcome.

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Key words: acute respiratory distress syndrome; high-frequency oscillation; high-frequency ventilation; mechanical ventilation; respiratory failure; severity of illness.

CONVENTIONAL mechanical ventilation (CMV) in patients with acute respiratory distress syndrome (ARDS) is a challenge. Alveolar collapse, cyclic lung reopening and overdistention during mechanical ventilation perpetuate alveolar injury (1). Presently, it is recommended to avoid high peak inspiratory pressures (PIP), large tidal volumes (TV) and high inspiratory oxygen concentration (FIo_2) (2, 3). Despite optimal use of CMV, progression of hypoxia and respiratory acidosis frequently occur. High frequency oscillatory ventilation (HFOV) is an alternative to CMV when oxygenation deteriorates. HFOV is usually defined as ventilation at frequencies of more than four times the normal frequency (4). At very high frequencies, elimination of carbon dioxide depends on the product of frequency and the square of tidal volume (4). Therefore, subdeadspace tidal volumes are possible. Peak pressures are reduced and collapsed lung segments may be recruited without causing alveolar overdistension and damage. In animals with induced hypoxemic lung failure, HFOV improves gas exchange, preserves surfactant and attenuates activation of alveolar inflammatory cells (5–8). In neonates with respiratory distress syndrome (RDS), HFOV reduces FIo_2 requirements, shortens the duration of oxygen therapy and lessens the incidence of acute and chronic lung disease compared to CMV (9, 10). In adult patients with ARDS, the use of HFOV is still considered investigational, and only two observational clinical trials have been published (11, 12).

Primarily, this study evaluates the safety, respiratory and circulatory measurements during HFOV in adult patients with severe ARDS failing conventional ventilation. Secondly, severity of illness and clinical outcome are studied.

Methods

Haukeland University Hospital is served by a 10-bed general ICU. Patients with burns are treated in a separate 8-bed burn unit. HFOV was introduced to treat severe hypoxemia in children with ARDS in 1995. From 1997 it has also been an option for adults with severe hypoxic respiratory failure and ARDS. HFOV is initiated if a Pao_2/FIo_2 ratio <13.0 kPa does not improve despite prone body position and optimal use of CMV. This study evaluates patients that received HFOV from August 1997 to March 2001. In this period, the total number of ICU patients aged >18 years was 1463. Mean Simplified Acute Physiology Score (SAPS II) was 43.9 and hospital mortality 31.0%. In the same period, there were 58 ARDS patients with a mean age 45.6 SD (20.4) years, SAPS II score 45.8 and hospital mortality 36.0%. ARDS was defined according to consensus guidelines (13). Since HFOV is an option for treating ARDS in our ICU, the treatment protocol for the study patients was not submitted to the ethical committee. Sixteen patients, mean age 38.2 (SD 17.5) (range 18–76) years, received HFOV and were included in the study and their observation forms with prospective sampled clinical data were evaluated and aggregated in retrospect. Patient characteristics are summarized in Table 1. All patients were treated with pressure controlled CMV (Evita 4 or Evita 2, Draeger Inc. Germany) before conversion to an adult high-frequency oscillator ventilator (Sensormedics 3100B, USA). Except for one patient (no. 14 with a tracheostomy) all were endotracheally intubated with tube size 8 mm (males) or 7 mm (females). Tracheal suction was performed using an in-

Table 1

Characteristics of ICU patients (n = 12) and burn patients (n = 4) with ARDS that received high frequency oscillatory ventilation (HFOV).

Pt.	Age	Weight	Sex	SAPS II	Cause of ARDS	Prior health	Marks during HFOV	Outcome
1	48	85	M	38	Pneumonia (*Legionella Pneumophilia*)		Relaxants used	S
2	26	70	M	23	Pneumonia (*Aspergillus Fumigatus*)	Mb. Chron (using immunosuppressive medicines)	Prone to supine position 12 h after HFOV-start. Steroids, relaxants used	D
3	50	70	M	44	Pneumonia (*Staphylococcus Milleri*)			S
4	43	62	F	23	Aspiration	Depressive disease	Relaxants used	S
5	42	71	F	50	Pneumonia/lung abscess (*Streptococcus Pneumoniae*)		Nitric oxide used 48 h after HFOV-start	S
6	38	84	M	32	Pneumonia (*Staphylococcus Aureus*)	Bronchial asthma		S
7	24	78	F	32	Pulmonary embolism/ sepsis postpartum		Prone to supine position 4 h after HFOV-start. Relaxants used	S
8	19	80	M	21	Pneumonia (*Hemophilus Influenzae*	Drug addiction	Nitric oxide used 48 h after. HFOV-start. Relaxants used	S
9	49	88	M	43	Pneumonia (*Pneumocystis Carinii*)	Weg. Granulomat. Depressive diesease	Steroids, relaxants used	S
10	56	57	F	57	Interstitial lung disease (induced of cytostatica)	Non-Hodg. lymfoma	Steroids used	D
11	76	63	F	46	Pneumonia	Cardial infarction 15 days ahead HFOV	Steroids, relaxants used	D
12	18	76	F	68	Pneumonia	Non-Hodg. lymfoma (use of cytostatica)	Relaxants used	D
13	21	73	M	44	Burn, inhalation injury/sepsis (*S. Aureus*)		Relaxants used	S
14	22	80	M	47	Burn, inhalation injury/sepsis (Acinetobacter)	Drug addiction		S
15	59	100	F	39	Burn, inhalation/injury/sepsis (*S. Aureus*)	Diabetes type II, Hypertension, Depressive disease	Relaxants used	S
16	20	90	M	37	Burn, inhalation injury/sepsis (Klebsiella, Enterobacter)	Bronchial asthma	Relaxants used	D
Mean (SD)	38.2 (17.5)	76.7 (11.7)		40.3 (12.6)				

Pt. = patients; SAPS II = Simplified Acute Physiology Score at ICU admission; S = 3-month survival; D = died; Relaxants = regularly administered neuromuscular blocking.
Values are mean (SD).

Table 2

Ventilator parameters 4 h after initiated high frequency oscillatory ventilation (HFOV) and at baseline (4 h prior to HFOV).

	Baseline	HFOV
FIo_2	0.78 (0.13)	0.64 (0.16)*
Mean airway pressure (cmH_2O):	23.7 (4.7)	29.4 (4.1)*
Peak inspiratory pressure (cmH_2O):	35.7 (4.8)	
Positive end expiratory pressure (cmH_2O):	11.8 (2.6)	
Frequency (min^{-1}):	18.3 (5.4)	
Tidal volume (ml):	579 (156)	
Pressure amplitude (cmH_2O):		64.9 (8.6)
Bias flow ($l min^{-1}$):		38.8 (4.9)
Frequency (Hz):		4.6 (0.8)

*$P < 0.05$ compared to baseline.
n = 15; values are mean (SD).

line catheter between the endotracheal tube and the ventilator circuit. A humidifier was placed in-line with the bias flow circuit. Adequate humidification was visually controlled by noting condensation along the inspiratory tubing. All had an indwelling arterial catheter and a central venous line.

Measurements

Four h prior to HFOV (baseline) and at 4, 8, 12, 24, 48 and 78 h after initiation of HFOV, Pao_2, FIo_2, $Paco_2$, pH, lactate, mean P_{aw}, mean arterial pressure (MAP), heart rate (HR) and central venous pressure (CVP) were measured. Cardiac output (CO), pulmonary artery occlusion pressure (PAOP) and oxygen delivery (Do_2) were recorded in three patients (no. 1, 5 and 8) who had an indwelling pulmonary catheter. Pao_2/FIo_2 ratio, oxygenation index (OI = mean $P_{aw} \cdot FIo_2 \cdot 100/Pao_2$) (11), was calculated at each interval. The number of days with the different ventilation modes and ventilator parameters were registered. SAPS II (14) was recorded on admission to the ICU, and Acute Physiology and Chronic Health Evaluation score (APACHE II) (15) at baseline. Sequential Organ Failure Assessment Score (SOFA) (16) was calculated at baseline and 24, 48 and 72 h after start of HFOV. Survival rate was recorded 3 months after start of HFOV.

Statistical analysis

Comparisons of measured variables over time in individuals were made by repeated measure analysis of variance (ANOVA). Comparisons between baseline data of survivors and non-survivors were determined by Mann–Whitney *U* rank sum test. All statistical calculations were performed using the SPSS 10.0 software package for windows. $P < 0.05$ was considered significant.

Results

The main causes of ARDS are summarized in Table 1. In the burn patients, the mean total body surface area affected by second- and/or third-degree burns was 49.3% (SD 18.4) (range 29–69). At baseline all patients had severe ARDS as noted by a mean Pao_2/FIo_2 ratio of 12.2 (SD 3.2) kPa, OI 28.1 (SD 12.6) cm H_2O $mmHg^{-1}$ and lung injury score (LIS) 3.2 (SD 0.3). Ventilator parameters before and after initiation of HFOV are summarized in Table 2. Mean ventilator time was 18.8 (SD 8.5) days, of which 6.3 (SD 2.9) days with HFOV. Conventional ventilation lasted 7.2 (SD 4.6) days before introduction of HFOV. Mean length of stay in hospital was 47.3 (SD 52.7) days, of which 24.9 (SD 17.4) days were in the ICU. In one patient, haemodynamic and respiratory data were omitted due to missing information.

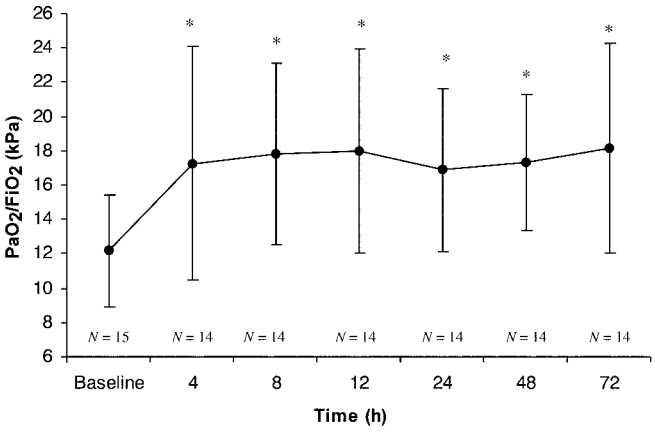

*Fig. 1. Pao_2/FIo_2 ratio during high frequency oscillatory ventilation (HFOV) and at baseline (conventional ventilation 4 h prior to HFOV). Values are mean (SD). *$P < 0.05$ compared to baseline.*

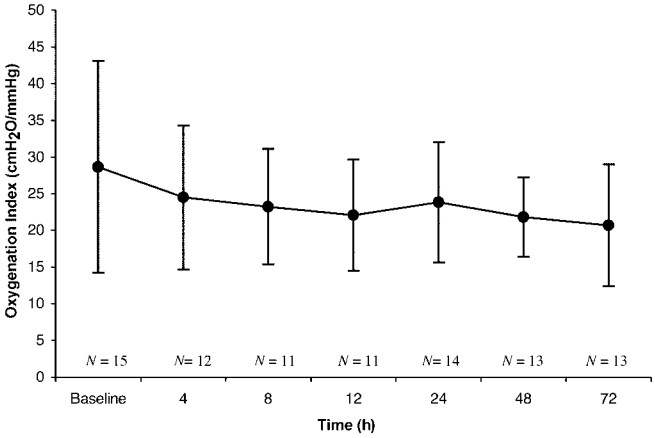

Fig. 2. Oxygenation index during high frequency oscillatory ventilation (HFOV) and at baseline (conventional ventilation 4 h prior to HFOV). Values are mean (SD).

Table 3

Respiratory and haemodynamic data during high frequency oscillatory ventilation (HFOV) and at baseline (4 h prior to HFOV).

	Baseline	4 h	12 h	24 h	72 h
Pao_2 (kPa)	9.2 ± 1.4 (15)	10.1 ± 1.7 (15)	9.8 ± 1.6 (14)	9.1 ± 1.5 (14)	9.5 ± 2.3 (14)
$Paco_2$ (kPa)	8.4 ± 1.8 (15)	8.8 ± 2.3 (15)	8.4 ± 2.8 (15)	8.6 ± 2.6 (14)	7.9 ± 1.9 (14)
pH	7.31 ± 0.09 (15)	7.31 ± 0.07 (15)	7.33 ± 0.10 (15)	7.32 ± 0.08 (14)	7.37 ± 0.11 (14)
Lactate (mmol l^{-1})	2.0 ± 1.1 (14)	1.8 ± 0.6 (14)	1.6 ± 0.5 (13)	1.7 ± 0.7 (13)	1.4 ± 0.4 (13)
MAP (mmHg)	67.2 ± 8.5 (15)	68.7 ± 8.1 (15)	69.9 ± 6.5 (15)	69.1 ± 7.9 (14)	70.7 ± 10.6 (14)
HR (beat min^{-1})	110 ± 17 (15)	112 ± 18 (15)	112 ± 21 (15)	111 ± 18(14)	108 ± 13 (14)
CVP (mmHg)	13.0 ± 2.9 (11)	13.3 ± 4.0 (10)	12.5 ± 4.1 (11)	12.6 ± 2.5 (11)	13.0 ± 3.6 (10)
CO (l min^{-1})	10.3 ± 3.2 (3)	10.2 ± 4.1 (3)	11.0 ± 3.7 (3)	9.5 ± 4.2 (3)	10.1 ± 6.1 (3)
Do_2 (l O_2 min^{-1})	1.23 ± 0.45 (3)	1.31 ± 0.59 (3)	1.34 ± 0.71 (3)	1.38 ± 0.68 (3)	1.22 ± 0.87 (3)
PAOP (mmHg)	15.0 ± 2.6 (3)	18.0 ± 3.6 (3)	16.3 ± 2.1 (3)	14.6 ± 2.6 (3)	15.5 ± 3.5 (3)

Values are mean ± SD.
Number of patients is in parentheses.

Gas exchange and mean P_{aw}. Within 4 h of HFOV, there was a significant reduction in FIo_2 ($P = 0.016$) compared to baseline (Table 2). Pao_2/FIo_2 ratio improved significantly by 4 h and remained elevated throughout the study period (Fig. 1). Compared to baseline, no significant difference was observed for Pao_2, $Paco_2$, lactate or pH (Table 3). This was observed both in non-survivors ($n = 5$) and survivors ($n = 11$) when studied separately. Mean P_{aw} significantly increased during transition from CMV to HFOV ($P < 0.001$) (Table 2). It was significantly higher for 48 h and was then gradually reduced toward baseline-level. OI demonstrated an insignificant reduction during HFOV compared to baseline (Fig. 2).

Haemodynamic variables. During HFOV, the haemodynamic variables (Table 3) demonstrated no significant changes compared to baseline. The requirement of vasoactive drugs and the fluid balance was not significantly changed during transition to HFOV.

Severity of illness. Mean SAPS II score on ICU admission was 40.3 (SD 12.6) (Table 1). APACHE II score at baseline was 26.6 (SD 4.3). Ending HFOV at 6.6 (SD 3.2) days, survivors significantly improved their SOFA scores compared to baseline (Fig. 3), non-survivors did not.

Survivors versus nonsurvivors. Prior to HFOV, no significant difference was found between survivors and nonsurvivors with regard to age, duration of ventilation, length of stay, gas exchange, haemodynamic parametres, severity of illness or ventilator parameters (Table 4).

Weaning, complications and outcome. One patient (no. 2) developed bilateral pneumothorax 5 days after the start of HFOV and one patient (no. 10) got bilateral pneumothorax during CMV shortly after ICU admission.

In the survivor group ($n = 11$), 10 patients were directly weaned from HFOV to CMV. They had a mean Pao_2/FIo_2 ratio of 19.9 (SD 5.1) kPa prior to the transition to CMV. These patients were discharged from the hospital without any ventilatory support. Six were transferred to their respective local hospitals or an institution for further rehabilitation, and four were discharged from the hospital ward to home. One patient did not improve oxygenation or OI and was transferred to an extracorporeal membrane oxygenation (ECMO) centre for further treatment. After 25 days on ECMO, this patient was weaned from conventional ventilation. Finally, after 16 more days without venti-

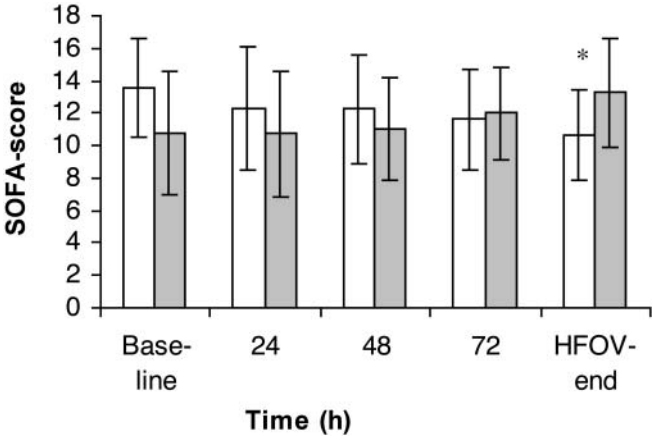

*Fig. 3. SOFA score during high frequency oscillatory ventilation (24, 48, 72 h, HFOV-end) and at baseline (conventional ventilation 4 h prior to HFOV) in survivors and nonsurvivors, who, respectively, ended HFOV after 6.6 (SD 3.2) and 5.4 (SD 2.2) days. (clear area) survivors ($n = 11$), (shaded area) nonsurvivors ($n = 5$). n was unchanged during study period. Values are mean (SD). *$P < 0.05$ compared to baseline.*

Table 4

Characteristics of survivors (n = 11) and nonsurvivors (n = 5) at baseline (4 h prior to HFOV) expressed as mean (SD).

	Survivors	Nonsurvivors
Days on conventional mechanical ventilation prior to HFOV	6.5 (4.9)	9.1 (3.5)
Days on HFOV	6.6 (3.2)	5.4 (2.2)
Age (years)	37.7 (14.0)	39.2 (25.6)
Weight (kg)	79.2 (10.3)	70.0 (14.4)
APACHE II	26.5 (4.6)	26.8 (3.8)
SOFA-score	13.5 (3.0)	10.8 (3.8)
LIS-score	3.1 (0.3)	3.4 (0.1)
pH	7.28 (0.08)	7.38 (0.09)
$Paco_2$ (kPa)	8.4 (1.1)	8.5 (3.3)
Lactate ($mmol\,l^{-1}$)	1.8 (0.7)	2.7 (1.8)
Pao_2/FIo_2 (kPa)	12.9 (3.2)	10.3 (2.9)
Oxygenation index (cmH_2O/mmHg)	25.4 (8.2)	35.6 (25.3)
Ventilator variables:		
Positive end expiratory pressure (cmH_2O)	11.5 (2.7)	11.8 (2.9)
Peek inspiratory pressure (cmH_2O)	34.3 (4.1)	38.3 (6.2)
Tidal volume (ml)	633 (142)	489 (177)

latory support, this patient was discharged from hospital to home.

In the nonsurvivor group (n = 5), three patients were successfully weaned off from HFOV. Mean Pao_2/FIo_2 ratio was 16.8 (SD 1.9) kPa before transition to CMV. Two patients received periodically external continuous positive airway pressure (CPAP) until withdrawal of care was decided due to poor cardial performance and malignancy. One patient (no. 12) was conventionally ventilated for several days until death from multiple organ failure (MOF). One patient (no. 2) was transferred to an ECMO centre. Eleven days after, he died from MOF. Patient no. 16 died of circulatory collapse and sepsis on the eighth day of HFOV.

Overall three-month survival was 68.8% (11/16).

Discussion

In the present study, we found improved oxygenation and reduced FIo_2 during HFOV compared to CMV. By 12 h of HFOV, Pao_2/Fio_2 ratio increased 47.6% compared to baseline. This may be explained in two ways. First, a significantly higher mean P_{aw} was applied when HFOV was instituted. Collapsed lung segments may then reopen and contribute in gas exchange (1). Second, during oscillation, at respiratory rates near the resonant frequency of the lung (5.0 Hz), tidal volumes can be lower than the dead space volume (4). Thereby, a constant airway pressure can be obtained which keeps the lung open throughout the respiratory cycle.

Our findings regarding oxygenation are consistent with those reported in two prospective non-randomized observational studies (11, 12), which report beneficial effects on oxygenation when a higher mean P_{aw} during HFOV compared to CMV is used. Additionally, these studies demonstrated a significant reduction in OI during HFOV, despite the higher mean P_{aw}. OI is an indicator of the mean airway pressure cost of oxygenation. It is used to define lung injury and reduced lung compliance, and it may be the most accurate tool to assess mortality in ARDS (11).

A second observation made in our study was the significant reduction of developing organ failure measured by SOFA score in survivors during HFOV. This may be because of the improved oxygenation associated with HFOV. Nonsurvivors also improved oxygenation during HFOV, but patients with immunosuppressive diseases and malignancies were included (Table 1), which may explain the deterioration of their SOFA score (Fig. 3). SOFA score is used daily in ICU patients to quantify organ dysfunction (16). Therefore, it may be a more dynamic measure to predict organ failure and outcome than SAPS II or APACHE II (14, 15), which is recorded only once during the first 24 h in the ICU.

The third main finding was the relatively high survival rate. Eleven of 16 patients (68.8%) were still alive 3 months after initiation of HFOV. The studies discussed above (11, 12) report overall survival rates of 47% and 33%, respectively, which exceed predicted survival based on APACHE II (15) at baseline in each of the trials. A possible lung protective role of HFOV may increase survival, in that high tidal volumes, peak airway pressures, alveolar overdistension and collapse are avoided (1, 4).

No changes in blood pressure and heart rate were

noted during transition to HFOV. Because most patients did not have a pulmonary artery catheter in place during the whole evaluation period, our data for PAOP, CO and Do_2 have limited value. Anyway, these parameters were unchanged during HFOV. The studies discussed above (11, 12) demonstrate a significant increase of PAOP 4–12 h after HFOV was initiated. The increased mean P_{aw} during HFOV is likely to explain this.

Comparing nonsurvivors with survivors prior to HFOV, no significant differences were revealed. Mean values differed much between the groups, but because of a small sample size, and hence wide standard deviations, no statistical changes were found (Table 4).

Extracorporeal membrane oxygenation (ECMO) may be indicated when ventilation modalities, including HFOV, fail (17). During the last 5 years, prospective trials have demonstrated encouraging results also when children and young adults with severe ARDS received ECMO (17–20). Because of larger study populations, these trials are more conclusive with regard to outcome with survival rates of 55–63%. Pre-ECMO Pao_2/FIo_2 ratios were then 6.5–7.8 kPa. Kolla and colleagues (18) reported in their study of 94 ARDS patients the following pre-ECMO ventilator parameters: PEEP: 14 cm H_2O and PIP: 47 cm H_2O. These data are consistent with those reported by Fort and colleagues in their study of HFOV in patients with ARDS (11).

Based on present data, HFOV may be an alternative ventilation mode in adult patients with ARDS when oxygenation deteriorates, despite optimal use of CMV and prone body position. Our results are promising, but should be evaluated with two constraints in mind. First, the number of study subjects is limited. Second, most data have been analysed retrospectively with no control group. Randomized studies in adults within this field have not been published.

High frequency oscillatory ventilation (HFOV) may have a lung protective role in patients with ARDS. Therefore, further trials should prospectively focus on ventilator associated lung injury and outcome when study subjects early in the course of ARDS are randomized to receive HFOV or CMV.

Conclusion

In adult patients with severe ARDS, HFOV can be used safely when conventional ventilation fails. Oxygenation effectively improves without haemodynamic compromise or increase of oxygenation index. SOFA score during HFOV may be a helpful tool to assess outcome. It is still uncertain whether HFOV compared to optimal CMV increases survival in ARDS patients with oxygenation failure.

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