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High-frequency oscillatory ventilation in adult acute respiratory distress syndrome

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Abstract *Objective:* This study examined whether ARDS patients in whom predefined ventilator settings fail to maintain oxygenation and CO_2 removal can be safely transitioned to high-frequency oscillatory ventilation (HFOV), and whether HFOV use is efficacious. *Design and setting:* Prospective observational study in the 14-bed intensive care unit of a university hospital. *Patients and participants:* 42 patients with ARDS (APACHE II score 28 (IQR 24–37) and ventilation time prior HFOV 3.0 days (0.7–9.1). *Measurements and results:* Gas exchange parameters and ventilator data were recorded before and during HFOV treatment (–12 h, –6 h, baseline, 10 min, 1 h, 6 h, 12 h, 24 h). Primary endpoints included: (a) P_aO_2/FIO_2 ratio 24 h after start of HFOV treatment or the last point of measurement if HFOV ended within the first 24 h; (b) HFOV-related complications. Post hoc analysis assessed the relationship between outcome and the re-sponse to HFOV, and between outcome and time of mechanical ventilation prior to HFOV. At baseline the median P_aO_2/FIO_2 ratio was 95 (IQR 62–129); after 24 h of HFOV the P_aO_2/FIO_2 ratio had increased significantly to 165 (88–225); only one patient developed a unilateral pneumothorax. Of the 42 patients 18 (43%) had died by day 30. Subset analyses showed a significantly higher 30-day mortality rate in patients with at least 3 days of mechanical ventilation prior to HFOV (64%) and in patients without oxygenation improvement after 24 h on HFOV (71%). *Conclusions:* HFOV is an effective and safe method to ventilate ARDS patients. Failure to improve oxygenation within 24 h of HFOV is associated with high mortality.

Keywords Adult respiratory distress syndrome · High-frequency oscillatory ventilation · Respiratory therapy · Ventilator-associated lung injury · Human

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by activation of inflammation and coagulation which induces changes in the permeability of the alveolocapillary membrane. As a result protein-containing fluid shifts into the interstitial and alveolar space. This leads to degradation of alveolar surfactant and to atelectasis formation, which results in increased intrapulmonary shunting and hypoxemia. Mismatch of ventilation and perfusion is further aggravated by microthrombosis of alveolar capillaries, resulting in increased alveolar dead space and P_aCO_2. It has recently been shown that the ventilation strategy used to manage patients with ARDS affects their outcome. There is good evidence that the ventilatory pattern itself can damage the lung and thereby perpetuate activation of inflammatory and coagulation pathways. These initially localized inflammatory processes in the lung may translocate through the blood to other organs, suggesting a progression to a systemic

inflammation syndrome and multiple organ system failure [1, 2, 3]. High inspiratory pressures and large tidal volumes leading to overdistension of the lung, cyclic alveolar collapse, and reopening during inspiration have all been identified as potential triggers of ventilator-induced lung injury [4, 5, 6, 7].

The current strategy of approaches with conventional mechanical ventilation in ARDS is to prevent further lung injury by high positive end-expiratory pressure (PEEP) levels to avoid end-expiratory lung collapse and by low tidal volumes to avoid overdistension. Often static pressure volume curves are used to determine lower and upper inflection points in order to adjust PEEP and end-inspiratory pressures above and below these points, respectively. There are limitations to these approaches when the pressure range between the upper and lower inflection points is too small to provide sufficient alveolar ventilation. It has also been shown that compartments with very long time constants (>8 s) may exist in patients with ARDS, and that such "slow" compartments may comprise more than 10% of aerated lung volume [8]. It is clear that compartments with time constants longer than 2–3 s are ventilated poorly using conventional respiratory rates.

High-frequency oscillatory ventilation (HFOV) is a technique that was first introduced into neonatal and pediatric intensive care. It uses molecular movement for oxygenation and effectively eliminates CO_2 by rapid (5–15 Hz) oscillatory swings of airway pressure around a mean positive airway pressure. In inhomogeneous lungs with some very long inspiratory time constants HFOV theoretically appears advantageous because the pressure swings are dampened during transmission to the alveoli, and the sustained high mean airway pressure may open slow-recruiting compartments and keep open fast-collapsing portions of the lungs [8].

The aim of this study was to assess the effectiveness and safety of HFOV in patients with ARDS in whom predefined ventilator settings failed to maintain oxygenation and CO_2 removal.

Materials and methods

This prospective observational study of an adult HFOV (Sensor-Medics 3100B, Yorba Linda, Calif., USA) was conducted at a single center. The study included all patients admitted to our ICU between January 1998 and April 2001 and fulfilling prospectively defined entry criteria on conventional ventilation (either Dräger EVITA4, Lübeck, Germany, or Siemens Servo300B, Erlangen, Germany). The investigational review board and the local ethics committee approved the study protocol, and informed consent was obtained for each patient from his/her legal representative prior to inclusion.

Study endpoints

Primary endpoints were: (a) The P_aO_2/FIO_2 ratio at 24 h after start of HFOV treatment or the last point of measurement if HFOV

Table 1 Characteristics of the overall population; data are absolute numbers or median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	n/Med	IQR
Gender: M/F	31/11	
Age (years)	49	35–58
Height (cm)	177	169–180
Body weight (kg)	80	66–91
Ventilation before HFOV (days)	3.0	0.7–9.1
HFOV duration (days)	1.2	0.3–2.3
APACHE II score	28	24–37
SAPS II	50	40–64
Tracheostomy (*n*)	9	–
Orotracheal tube (*n*)	33	–
Tube diameter (mm)	8.0	8.0–8.5

ended within the first 24 h and (b) the number of HFOV-related complications (mucus obstruction, pulmonary air leak, or arterial hypotension). Secondary endpoints were: (a) 30-day mortality and (b) relationship between endpoint outcomes and HFOV treatment response. Post hoc analyses assessed the pre-HFOV time on mechanical ventilation and endpoint outcomes.

Patient selection

The study included all 42 consecutive patients treated for HFOV between January 1998 and April 2001 (Table 1) who met the following criteria: failure of conventional mechanical ventilation, informed consent of legal representative, no heart failure, no severe obstructive lung disease, HFOV available, and body weight 35 kg or more. Failure of conventional ventilation was defined as P_aO_2/FIO_2 ratio less than 200 mmHg and no improvement in oxygenation following 2 h of optimized pressure-controlled ventilation (PCV). Improvement in oxygenation was defined as an increase in P_aO_2/FIO_2 ratio of at least 50. Exclusion criteria were: lack of informed consent, pregnancy, anticipated death, and withdrawal of life support because of poor prognosis within 24 h. The most frequent diagnoses were pneumonia ($n=30$) and systemic inflammatory response syndrome (SIRS) resulting from trauma or infection ($n=24$; Table 2). Baseline median Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 28 [interquartile range (IQR) 24–37] and Simplified Acute Physiology Score (SAPS) was 50 (40–64). Twenty-three patients had multiple-organ system failure, and 18 required continuous venovenous hemofiltration.

Pre-HFOV ventilator settings on PCV were allowed to a maximum PEEP of 15 cmH₂O and a maximum inspiratory airway pressure (P_{max}) of 35 cmH₂O. Respiratory rate and I:E ratio were set as to avoid intrinsic PEEP (monitored by expiratory flow tracings) while allowing an inspiratory time of more than 1.5 s. A rise in P_aCO_2 was permitted as long as an arterial pH was 7.20 or higher. Recruitment maneuvers were routinely performed on all patients on PCV. The recruitment procedure for optimization of aerated lung volume was performed by switching the ventilator to the CPAP mode and adjusting CPAP to 40 cmH₂O for 30 s. PEEP was then increased by 3–5 cmH₂O above the initial value. If the procedure showed an improvement in oxygenation, it was repeated up to a maximum PEEP of 15 cmH₂O. If 2 h after "optimized" conventional PCV the P_aO_2/FIO_2 ratio had not increased by 50, and the patient fulfilled all other inclusion criteria, he/she was transitioned to HFOV.

Table 2 Diagnosis at baseline

	n
Pneumonia	30
Gram-negative	5
Gram-positive	9
Fungal	2
Viral	1
Other	4
Unknown agent	7
Gastric aspiration	2
SIRS sepsis	24
Gram-negative	4
Gram-positive	3
Fungal	2
Unknown agent	10
Not infected	5
Multiple organ system failure	23
Acute renal failure	18
Renal replacement	14
Multiple trauma	7
Disseminated intravascular coagulation	5
Increased intracranial pressure	4
Paralytic ileus	3
Organ transplantation	3
Liver/lung	2
Bone marrow	1

HFOV settings

For transition to HFOV the following initial settings were used: FIO_2 of 1.0, continuous distending pressure (CDP) 5 cmH_2O above the last measured mean airway pressure on conventional ventilation, inspiratory time at 33% of total respiratory cycle; oscillatory frequency at 5 Hz; bias flow at 30 l/min; oscillatory amplitude (ΔP) scaled relative to entry P_aCO_2. To improve oxygenation during HFOV lung volume was recruited by a stepwise increase in CDP to a maximum of 40 cmH_2O. After each step P_aO_2 and its trend were assessed, and CDP was increased as long as P_aO_2 increased. If P_aO_2 decreased after raising CDP, we analyzed the trend in P_aO_2. A positive trend was considered as slow recruitment, and the CDP level was maintained. A decrease in P_aO_2 without a positive trend was interpreted as no further recruitment, and overdistension of open lung units and CDP was reduced. A closed in-line suction system was used (TrachCare DSE, Kendall, Germany) to avoid disconnection with abrupt loss of mean airway pressure and lung volume.

After achieving maximum recruitment using this strategy the lowest possible CDP was selected that would keep the lung open. This was determined by stepwise reductions in CDP to the point at which collapse of alveolar units became evident from a decrease in P_aO_2. CDP was then adjusted to 2–3 cmH_2O above this pressure. The targeted P_aCO_2 range was between 35 and 80 mmHg, with an arterial pH greater than 7.20 and arterial bicarbonate of more than 19 mmol/l. P_aCO_2 was adjusted by increasing oscillatory amplitude (ΔP). If hypercapnia persisted despite an oscillatory amplitude of more than 90 cmH_2O, oscillatory frequency was reduced in steps of 0.5 Hz, to a lower limit of 3 Hz. During HFOV treatment patients were sedated to a level which suppressed spontaneous respiration, since technical limitations of HFOV at that time did not allow spontaneous breathing.

Measurements

Ventilator settings, hemodynamic, and gas exchange data were recorded at time points before (–12 h, –6 h, –10 min) and during (10 min, 1 h, 6 h, 12 h, 24 h) HFOV treatment. Airway pressures (P_{max}, P_{mean}, PEEP, CDP, ΔP) and ventilator settings (FIO_2, respiratory rate, tidal volume, inspiratory time, oscillatory frequency, bias flow) were read directly from the ventilator. Continuous blood gas analysis by an intra-arterial multiparameter sensor (Paratrend 7) was used in most patients. Intermittent conventional blood gas analyses were performed for calibration of the continuous sensor or if no continuous measurement was available. The P_aO_2/FIO_2 ratio and oxygenation index $[(P_{mean}\times FIO_2\times 100)/P_aO_2]$ were calculated for the defined recording period. Invasive hemodynamic data were recorded from an indwelling arterial line. The data recorded 10 min before transition to HFOV were defined as baseline for comparison with other points of measurement.

The APACHE II score and SAPS II were calculated for the 24 h period before the start of HFOV treatment. We also recorded duration of ventilation before, during, and after HFOV, length of stay in ICU and in the hospital, the cause of critical illness, concomitant diseases, and causes of mortality. During HFOV patients were monitored for the following adverse events: mucus obstruction, pulmonary air leak and, arterial hypotension. Hypotension was defined as a mean arterial pressure of less than 60 mmHg for 2 h after changing to HFOV or related to an increase in CDP during HFOV. HFOV treatment was stopped if hypotension remained unresponsive to optimization of filling pressures, vasoactive and/or inotropic support. Patients who failed to improve their oxygenation (despite increased CDP up to 40 cmH_2O and FIO_2 up to 1.0) defined as an increase in the P_aO_2/FIO_2 ratio of less than 50 after 24 h of treatment or failed ventilation (P_aCO_2 ≥80 mmHg, pH <7.20, bicarbonate ≤19 mmol/l) during HFOV (HFOV failure) were returned to conventional PCV or underwent screening for the eligibility for extracorporeal membrane oxygenation.

General intensive care included parenteral and/or enteral nutrition, administration of fluids and, if required, inotropic and vasopressor agents. Cumulative 24-h fluid balance was targeted to be zero or negative. Renal failure was treated with continuous venovenous hemofiltration. Prone positioning was used regularly. Neuromuscular blocking agents were not used. Drugs used for sedation included sufentanil, midazolam and propofol. We recorded the occurrence of SIRS and infectious process sepsis syndrome (positive blood culture, latex agglutination test, or other equivalent tests) if at least two of the following clinical conditions were present: body temperature higher than 38°C or lower than 36°C; heart rate above 90 beats/min; white blood cell count greater than 12,000/μl or less than 4,000/μl and/or immature band forms more than 10%, respiratory rate above 20 breaths/min or P_aCO_2 lower than 32 mmHg. Presence of multiple-organ failure was defined if more than one organ showed acute dysfunction and hemostasis could not be maintained without intervention. Acute renal failure was present when glomerular filtration rate suddenly decreased as demonstrated by a progressive rise in creatinine and blood urea nitrogen and accompanied by anuria, oliguria or polyuria, and electrolyte imbalance.

Weaning from HFOV

Immediately after reaching a stable state on HFOV weaning started, first, by reduction in FIO_2 and, second, by stepwise reduction in CDP guided by continuous or frequent intermittent blood gas analysis. Patients with improved and stable oxygenation requiring a FIO_2 of less than 0.6 and a CDP less than 25 cmH_2O were weaned to conventional PCV. PCV settings after weaning from HFOV were selected according to the final CDP level on HFOV. After successful HFOV weaning the first priority was initiation of spontaneous breathing efforts.

Table 3 Pressure-controlled ventilator settings before HFOV; data are median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	12 h (n=22)		6 h (n=35)		Baseline (n=42)	
	Med	IQR	Med	IQR	Med	IQR
PCV P_{max} (cmH$_2$O)	30	28–38	34	29–37	35	30–38
PCV PEEP (cmH$_2$O)	10	8–16	15	10–16	15	10–16
PCV P_{mean} (cmH$_2$O)	21	16–25	24	18–25	24	19–25
FIO$_2$	0.7	0.5–1.0	1.0*	0.6–1.0	1.0*	0.8–1.0
Tidal volume (ml/kg)	6.3	5.0–8.0	6.7	4.7–8.3	6.6	5.0–8.4
Tidal volume (ml/kg IBW)[a]	6.8	5.9–8.1	6.8	5.6–8.2	6.7	5.6–8.5
Respirator rate (b/min)	19	17–23	18.0	15–25	18.0	15–20
Inspiratory time (%)	45	40–50	50	40–50	50	40–50
P$_a$O$_2$/FIO$_2$ ratio	155	122–173	84	64–171	94*	62–129
Oxygenation index[b]	14	9–22	24	12–38	23*	16–36
P$_a$CO$_2$ (mmHg)	56	45–68	56	47–74	57	44–76
Arterial pH	7.32	7.24–7.43	7.33	7.21–7.41	7.33	7.22–7.40
Bicarbonate (mmol/l)	29.8	25.0–33.0	29.2	25.0–31.8	28.0	25.0–32.0

Statistical analysis

Data are given as median and IQR. Intra-individual effects of HFOV and PCV upon gas exchange and mean arterial pressure were compared using nonparametric testing (Wilcoxon sign rank test), with Bonferroni's correction for multiple testing. Subgroup analyses compared 30-day mortality, APACHE score, demographics, and gas exchange in the following subsets of patients: (a) two groups defined by a stable increase in the ΔP$_a$O2/FIO$_2$ ratio of at least 50 or by a ΔP$_a$O$_2$/FIO$_2$ ratio less than 50 mmHg following 24 h of HFOV treatment (or the last measurement if HFOV ended within the first 24 h); (b) two groups based on length of mechanical ventilation prior to HFOV, less than 3 days vs. 3 days or longer.

Intergroup differences in demographics, gas exchange, and ventilator settings were analyzed using the Wilcoxon/Mann-Whitney *U* test. Both effects (response to HFOV treatment and length of ventilation) were compared for differences in mortality by Kaplan-Meier survival analysis and the log-rank test (Peto-Pike and Cox-Mantel). A *p* value less than 0.05 was considered statistically significant.

Fig. 1 Median P$_a$O$_2$/FIO$_2$ ratio (*circles*) and oxygenation index (*squares*) with 25th and 75th percentiles for all patients (*n*=42) at baseline and at 12 h or, if earlier, at first point of measurement prior to HFOV initiation. Wilcoxon signed rank test

Results

Patients were on PCV for a median of 3.0 days (IQR 0.7–9.1) prior to HFOV. The median duration of HFOV support was 1.2 days (0.3–2.3). The HFOV duration of seven patients were less than 6 h. Three of these responded quickly to HFOV treatment and were transitioned to the PCV while three others were switched back to PCV because oxygenation worsened (one was transitioned to the extracorporeal membrane oxygenation), and one was switched back for surgical treatment in the operating theater. Within 24 h 18 patients were taken off from HFOV. Five of these died (intractable bleeding, progressive septic shock), seven responded quickly to HFOV, five worsened in oxygenation, and one required a surgical treatment.

Primary study endpoint: improvement in oxygenation

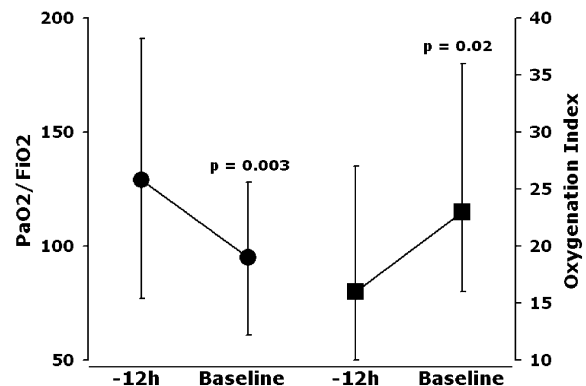Table 3 presents PCV settings 12 and 6 h prior to HFOV and at baseline (10 min prior to HFOV). The P$_a$O$_2$/FIO$_2$ ratio showed a progressive deterioration prior to HFOV and at transition was 95 (IQR 62–129). The oxygenation index worsened within the 12 h period prior to initiating HFOV from 14 (9–22) to 23 (16–36) at baseline (Fig. 1). The median P$_a$O$_2$/FIO$_2$ ratio increased significantly (*p*<0.000001) from the baseline of 95 (62–129) to 165 (88–225) within the first 24 h of HFOV or at the last point of measurement if HFOV ended within the first 24 h (Fig. 2). P$_a$CO$_2$ could be maintained within the target range except in one patient. Five patients required an oscillatory rate of 3–4 Hz to achieve the target P$_a$CO$_2$, and the maximum duration of this was 6 h. Detailed HFOV settings during the first 24 h are shown in Table 4.

Primary study endpoint: HFOV adverse events

There was no endotracheal tube obstruction by mucous plugs. One patient developed a unilateral pneumothorax during HFOV requiring placement of a chest tube. The
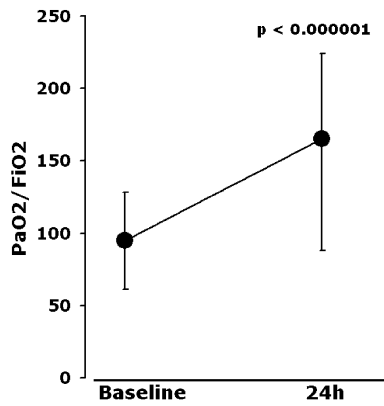
Fig. 2 Primary study endpoint: P_aO_2/FIO_2 ratio (median with 25th and 75th percentiles) for all patients ($n=42$) at baseline and after 24 h of HFOV treatment or, if HFOV ended within the first 24 h, at the last point of measurement. Wilcoxon signed rank test

pneumothorax was not associated with impairment in oxygenation or ventilation, and HFOV was continued. There was no unresponsive arterial hypotension defined as a mean arterial pressure less than 60 mmHg for 2 h. The four trauma patients with intracranial pressure monitoring showed no deterioration during HFOV treatment.

Secondary study endpoint: 30-day mortality

Of the 42 patients 18 (43%) died within 30 days following inclusion (Table 5). Six of these died from respiratory causes, and 12 were nonrespiratory deaths (e.g., multiple organ system failure, intractable bleeding, brain death), 5 of whom had life support withdrawn. Overall hospital mortality of the entire patient cohort was 52% (22/42).

Table 4 HFOV settings, gas exchange, and mean arterial pressure; data are median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	Start ($n=42$)		1 h ($n=42$)		6 h ($n=35$)		12 h ($n=30$)		24 h ($n=24$)		End ($n=42$)	
	Med	IQR	Med	IQR	Med	IQR	Med	IQR	Med	IQR	Med	IQR
CDP (cmH$_2$O)	30*	26–34	30*	25–34	30*	24–32	30*	26–34	31*	24–35	27*	20–32
ΔP (cmH$_2$O)	70.0	59.5–87.0	70.0	82.0–86.0	70.0	58.0–85.0	71.0	59.5–87.3	70.0	58.5–85.3	70.0	(60.0)
Frequency (Hz)	5.0	5.0–5.0	5.0	4.6–5.0	5.0	4.5–5.0	5.0	4.5–5.0	5.0	4.6–5.0	5.0	4.5–5.0
Inspiratory time (%)	33	33–33	33	33–33	33	33–35	33	33–35	33	33–35	33	33–38
FIO$_2$	1.0	1.0–1.0	1.0	0.8–1.0	0.8*	0.6–0.9	0.7*	0.5–0.9	0.6*	0.5–0.8	0.6*	0.5–1.0
P$_a$O$_2$/FIO$_2$ ratio	99*	73–166	119*	81–182	135*	91–211	184*	133–233	168*	126–230	214*	78–279
Oxygenation index[a]	31	14–43	27	16–40	22*	12–30	17*	12–27	15	10–26	12*	7.5–35
P$_a$CO$_2$ (mmHg)	54	44–76	57	48–70	52	43–70	54	41–74	48	38–57	51	45–65
MAP (mmHg)	77	69–85	76	66–86	80	69–88	81	71–90	79	73–89	81	69–91

* $p<0.05$ vs. baseline values prior HFOV (multiple Wilcoxon sign-rank tests with Bonferroni's post hoc test)
[a] (Mean airway pressure×FIO$_2$×100)/P$_a$O$_2$

Table 5 Baseline comparison: 30-day survivors vs. nonsurvivors; data are median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	Nonsurvivors ($n=18$)		Survivors ($n=24$)		p[a]
	Med	IQR	Med	IQR	
HFOV duration (days)	0.8	0.3–2.0	1.7	0.8–3.0	0.10
APACHE II score[b]	34	26–40	26	22–35	0.037
SAPS II[b]	60	49–70	41	29–60	0.001
PCV P$_{max}$ (cmH$_2$O)	36	31–40	34	30–38	0.08
PCV PEEP (cmH$_2$O)	15	10–17	14	10–15	0.56
PCV P$_{mean}$ (cmH$_2$O)	24	19–27	22	19–25	0.22
FIO$_2$	1.0	1.0–1.0	1.0	0.8–1.0	0.13
Respirator rate (/min)	17	16–21	20	15–20	0.99
Tidal volume (ml/kg)	6.1	4.6–7.8	7.3	5.7–8.4	0.21
Tidal volume (ml/kg IBW)[c]	6.4	4.9–7.9	6.8	6.1–9.7	0.08
Inspiration time (%)	50	40–50	50	40–50	0.37
P$_a$O$_2$/FIO$_2$ ratio	67	53–91	115	67–153	0.013
Oxygenation index[d]	33	27–49	18	15–30	0.012
P$_a$CO$_2$ (mmHg)	60	49–74	56	43–79	0.75

[a] Wilcoxon/Mann-Whitney U test
[b] Calculated for the 24 h before the start of HFOV treatment
[c] Ideal body weight=25×(height in meters)^2
[d] (Mean airway pressure×FIO$_2$×100)/P$_a$O$_2$

Subset analysis

Outcome effect of oxygenation response to HFOV

The time course of the $\Delta P_aO_2/FIO_2$ ratio for the 42 patients was analyzed for the first 24 h of HFOV. In 25 (responder group) there was a stable increase in $\Delta P_aO_2/FIO_2$ ratio of at least 50, 24 h after start of HFOV compared to the baseline values. Seventeen patients (nonresponder group) failed to meet the $\Delta P_aO_2/FIO_2$ ratio criteria. After 30 days 6 of the 25 responders (24%) and 12 of the 17 nonresponders (71%) died. The results
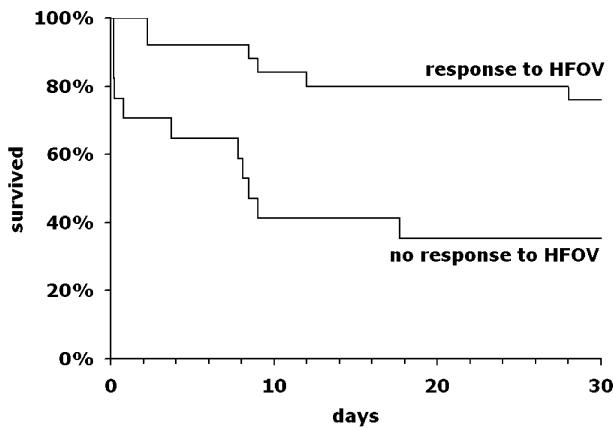
Fig. 3 Thirty-day mortality according to HFOV oxygenation response. Responders: stable increase in $\Delta P_aO2/FIO_2$ ratio of 50 or more after 24 h of HFOV or at the last point of measurement if HFOV ended within the first 24 h. Nonresponders: $\Delta P_aO2/FIO_2$ ratio less than 50 increase after 24 h of HFOV or at the last point of measurement if HFOV ended within the first 24 h. Log-rank test: Peto-Pike $p=0.001$, Cox-Mantel $p=0.001$

of the log-rank test and the Kaplan-Meier trace are shown in Fig. 3. There were significant differences between responders and nonresponders in SAPS, P_{max}, P_aO2/FIO_2 ratio, and oxygenation index at baseline (Table 6). The median duration of HFOV treatment was 1.9 days (IQR 1.0– 3.4) in responders and 1.0 days (0.4– 1.2) in nonresponders ($p=0.0004$).

Outcome effect of mechanical ventilation time prior to HFOV

At baseline 20 of the 42 patients had been on PCV less than 3 days and the other 22 3 days or longer. The 30-day mortality was 64% in patients with longer 3 days ventilation before HFOV treatment and 20% in those with shorter ventilation support. Figure 4 shows the
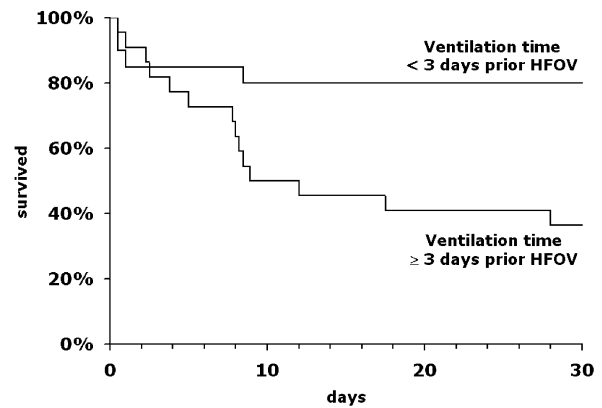
Fig. 4 Thirty-day mortality: days of pre-HFOV mechanical ventilation. Log-rank test: Peto-Pike $p=0.02$, Cox-Mantel $p=0.01$

Table 6 Baseline comparison: group with response to HFOV vs. group without response; data are median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	Response[a] (n=25)		No response[b] (n=17)		p[c]
APACHE II score[d]	27	23–34	34	26–39	0.07
SAPS II[d]	44	37–60	62	47–72	0.01
PCV P_{max} (cmH$_2$O)	32	30–35	38	34–40	0.01
PCV PEEP (cmH$_2$O)	14	10–16	14	10–17	0.74
PCV P_{mean} (cmH$_2$O)	22	18–25	24	22–26	0.07
FIO$_2$	1.0	0.8–1.0	1.0	0.9–1.0	0.30
Respirator rate (/min)	20	15–20	17	15–25	0.78
Tidal volume (ml/kg)	6.5	5.2–8.3	7.6	4.5–8.6	0.88
Tidal volume (ml/kg IBW)[e]	6.8	5.9–8.6	6.6	5.1–8.6	0.58
Inspiration time (%)	50	40–50	50	40–50	0.47
P_aO_2/FIO_2 ratio	105	65–146	70	52–108	0.04
Oxygenation index[f]	18	14–33	32	25–49	0.01
P_aCO_2 (mmHg)	58	48–75	54	45–78	0.95

[a] Response to HFOV includes patients with stable increase in $\Delta P_aO2/FIO_2$ ratio of 50 or more after 24 h of HFOV or at the last point of measurement if HFOV ended within the first 24 h

[b] Without response to HFOV includes patients with a $\Delta P_aO2/FIO_2$ ratio of less than 50 after 24 h of HFOV or at the last point of measurement if HFOV ended within the first 24 h

[c] Wilcoxon/Mann-Whitney U test

[d] Calculated for the 24 h period before the start of HFOV treatment

[e] Ideal body weight=25×(height in meters)^2

[f] (Mean airway pressure ×FIO$_2$×100)/P_aO_2

Kaplan-Meier 30-days survival traces for different durations of ventilator support prior to HFOV and the result of the log-rank test (Cox-Mantel $p=0.01$, Peto-Pike $p=0.02$). At baseline there was no difference in demographics, APACHE II, ventilator settings or P_aO_2/FIO_2 ratio between these groups. The duration of HFOV treatment showed no significant differences between the groups.

Discussion

The benefits accruing from reduced delivered volumes have been appreciated during the period since the National Institutes of Health ARDS Net trial [9] comparing low vs. large tidal volumes. Since HFOV delivers only very small tidal volumes, it therefore appears theoretically to be an ideal ventilation strategy in ARDS. In our observational study we transitioned patients failing a strategy of conventional ventilation to HFOV and evaluated their treatment response during the subsequent 24 h and their in-hospital outcome.

All patients in this study had severe oxygenation failure before HFOV was initiated. The P_aO_2/FIO_2 ratio in all patients was below 200 at baseline and in more than 80% was below 150. Peak inspiratory pressures of PCV at baseline (35 cmH2O) were near the maximum value of the published "secure window" for mechanical ventilation [4, 5, 6, 7, 10, 11], and high PEEP was used. The patients included in this study had higher FIO_2, higher mean airway pressure, higher PEEP level, and lower P_aO_2/FIO_2 ratio at baseline than those in the HFOV group reported in the recent MOAT trial [12]. Despite these high levels of ventilatory support with PCV oxygenation subsequently worsened, and FIO_2 requirements increased significantly over 12 h preceding HFOV. The tidal volumes during PCV at baseline were close to the recommended settings of the ARDS Net trial [9], and permissive hypercapnia was part of the concept.

After initiating HFOV mean airway pressures were initially increased by 5 cmH$_2$O and finally optimized at 8 cmH$_2$O above PCV baseline setting according to the study design. It remains uncertain whether further sustained increases in mean airway pressure during PCV would have led to a similar improvement in oxygenation, although recruitment maneuvers using pressures equivalent to the HFOV CDP were attempted but without beneficial response. Additionally, in this protocol a further increase in PEEP would have required higher peak inspiratory pressures at the risk of overdistension and barotrauma. At baseline peak inspiratory pressures were at the prospectively defined limit of 35 cmH$_2$O in 71% of patients (30/42). Our HFOV protocol allowed applying high mean airway pressures and avoided high inspiratory pressures and cyclic end-expiratory lung collapse with reopening on inspiration. The MOAT trial [12] compared the two ventilation techniques and reported a similar increase in oxygenation in HFOV and in conventionally treated patients. However, the course of the P_aO_2/FIO_2 ratio in the conventionally treated patients showed a delayed increase after 8 and 16 h of treatment compared to the HFOV cohort.

The P_aO_2/FIO_2 ratio in this study showed an early improvement in oxygenation, with a first peak after 12 h of treatment and a slight decrease after 24 h of HFOV. A similar time course in oxygenation was reported in the MOAT trial [12], but its cause remains unclear. The oxygenation index has been used in neonatal and adult literature as a marker of "pressure cost of oxygenation." In contrast to the rapid improvement in the P_aO_2/FIO_2 ratio after HFOV initiation, the change in oxygenation index was slower and became significant only after 6 h (Table 4). This is apparently due to the high mean airway pressure required to improve oxygenation. A similar delay in improvement in oxygenation index vs. the P_aO_2/FIO_2 ratio was reported by Mehta et al. [13].

HFOV duration was less than 6 h in seven patients. Three of these responded quickly to HFOV treatment and were switched to PCV; three others were returned to PCV because oxygenation worsened (one underwent extracorporal membrane oxygenation), and one whose oxygenation responded to HFOV had to be returned to a conventional ventilator when undergoing surgery in the operating theater. Eighteen patients in all were taken off HFOV within 24 h; seven of these responded quickly to HFOV, one underwent surgery, five experienced worsened oxygenation, and five patients died from intractable bleeding or progressive septic shock.

Factors affecting 30-day mortality

The published mortality rate of patients with ARDS ranges widely from 10% to 90%. Due to the small number of studies of adults with ARDS treated with HFOV and the differences between treatment protocols, comparison to our findings is limited. There have been only two recent prospective nonrandomized trials of HFOV in adults with ARDS, one controlled randomized multicenter trial in which 30-day mortality was assessed, and one retrospective study which analyzed both 3-month mortality and possible contributors [12, 13, 14, 15].

Fort and colleagues [14] treated 17 patients with severe ARDS with HFOV. After 30 days 9 of the 17 (53%) had died. Four of the nonsurvivors died from oxygenation failure and the other five from nonrespiratory related factors (multiple-organ system failure or bleeding). Mehta et al. [13] treated 24 ARDS patients with HFOV and reported a 30-day mortality of 67%. The mortality from respiratory causes in this study was very low (6.7%). A retrospective investigation by Andersen et al. [15] in 16 patients with ARDS and HFOV treatment re-

Table 7 Baseline comparison: group with less than 3 days on mechanical ventilation vs. group with 3 days or more; data are median (*Med*) and interquartile range (*IQR*, 25th–75th percentiles)

	<3 days (n=20)		≥3 days (n=22)		p^a
	Med	IQR	Med	IQR	
HFOV duration (days)	1.6	0.5–2.0	1.0	0.25–3.0	0.99
APACHE II Score[b]	27	24–32	33	26–37	0.21
SAPS II	42	37–61	57	46–67	0.08
PCV P_{max} (cmH$_2$O)	35	30–38	35	30–38	0.95
PCV PEEP (cmH$_2$O)	14	10–15	14	10–17	0.76
PCV P_{mean} (cmH$_2$O)	22	19–25	24	19–26	0.43
FIO$_2$	1.0	1.0–1.0	1.0	0.8–1.0	0.15
Respirator rate (/min)	17	15–20	19	16–23	0.21
Tidal volume (ml/kg)	7.1	6.1–8.4	6.1	4.8–8.2	0.31
Tidal volume (ml/kg IBW)[c]	7.8	6.1–8.8	6.2	5.1–8.2	0.07
Inspiration time (%)	50	43–50	50	40–50	0.62
P_aO_2/FIO$_2$ ratio	93	52–123	95	64–166	0.23
Oxygenation index[d]	22	17–46	26	15–34	0.45
P_aCO_2 (mmHg)	59	44–78	56	44–75	0.83

[a] Wilcoxon/Mann-Whitney *U* test
[b] Calculated for the 24 h period before the start of HFOV treatment
[c] Ideal body weight=25×(height in meters)^2
[d] (Mean airway pressure× FIO$_2$×100)/P_aO_2

ported a 3-month mortality of 31%. All investigations also used an initially higher CDP of up to 5 cmH$_2$O more than the mean airway pressure of the PCV at baseline. They also reported significant improvements in oxygenation and reduction in FIO$_2$ requirements during HFOV. The randomized, controlled MOAT trial [12] compared HFOV with a conventional ventilation strategy in adults with ARDS; HFOV was associated with a nonsignificant trend to reduced 30-day mortality (HFOV 37%, conventional ventilation strategy 52%).

The 30-day mortality in the current study was 43% and thus comparable to that reported by Fort et al. [14] and in the MOAT trial [12]. The majority of deaths in our study were due to factors unrelated to the respiratory system (67%). These findings are similar to those of recent reports in which death in ARDS patients appeared to be more closely associated with multiple-organ dysfunction than pulmonary origin [16, 17, 18].

After patient inclusion the individual APACHE II score in the current investigation was determined for the 24 h period prior HFOV implementation and therefore does not necessarily reflect the prognosis of the patients. APACHE II score and SAPS were used for the comparative evaluation of the individual degree of illness. We found a significant difference at baseline in APACHE II score, SAPS, oxygenation index, and P_aO_2/FIO$_2$ ratio between the 30-day survivors and nonsurvivors (Table 5). Nonsurvivors were sicker at baseline as reflected by their higher APACHE II score and SAPS. Additionally, nonsurvivors had lower entry P_aO_2/FIO$_2$ ratios and higher oxygenation indices, suggesting a more severe pulmonary dysfunction.

The average APACHE II scores reported by Fort et al. [14] and Mehta et al. [13] range between 23.3±7.5 and 21.5±6.9. Despite lower APACHE II scores the 30-day mortality reported by Mehta et al. was higher, but their cohort included several patients with malignant disease, bone marrow transplantation, and burns associated with high mortality. The MOAT trial [12] found no difference in APACHE II scores between HFOV and conventionally treated patients, their APACHE II scores ranging around 22 in both groups.

A randomized controlled trial in pediatric ARDS patients has shown that early use of HFOV reduces the severity of the clinical course and improves patient outcome [19]. Our results demonstrated a significantly higher 30-day mortality in patients on conventional ventilation of 3 days or longer prior to HFOV, similar to the findings of Mehta et al. [13] and Fort et al. [14]. We found no difference in demographics, APACHE II score, SAPS, ventilator settings, oxygenation index, or P_aO_2/FIO$_2$ ratio at baseline between these groups of patients (Table 7). We have two hypotheses to explaining this finding: (a) patients with ARDS respond better to HFOV when it is implemented earlier, (b) patients on mechanical ventilation for more than 3 days have a higher severity of illness as reflected by a nonsignificant trend to different SAPS. An earlier study demonstrated the association between mortality and duration of mechanical ventilation prior to onset of ARDS [20]. Our cutoff at 3 days of ventilation before HFOV was arbitrary but was based on unpublished data from the pediatric ARDS trial [19] that reported a 25-fold increase in risk of chronic lung disease for survivors transitioned to HFOV after 72 h.

In our study patients whose oxygenation failed to improve within 24 h after initiation of HFOV had a significantly higher 30-day mortality than patients whose gas exchange did improve. Between these groups we found significant differences in SAPS, ventilator settings, oxygenation index, and P_aO_2/FIO$_2$ ratio at baseline. The higher APACHE II score and SAPS and worse baseline oxygenation in patients without response to HFOV reflects more severe illness and pulmonary dysfunction in this subgroup. The duration of HFOV differed significantly, but 5 of the 17 patients without response to HFOV

died during the first 24 h of treatment. The main reasons for mortality in these patients were intractable bleeding and progressive septic shock. Mehta and colleagues [13] defined improved oxygenation as an increase in the P_aO_2/FIO_2 ratio of more than 20% at 8 and 24 h on HFOV. They found no significant differences in baseline characteristics between their patients with and those without improved oxygenation during HFOV treatment, and their 30-day mortality was similar to that which we found. Fort and colleagues [14] reported an improvement in oxygenation but without defining it; however, they also observed higher 30-day mortality in patients whose oxygenation failed to improve (54%) than in those with improved oxygenation (12%). An increase in the P_aO_2/FIO_2 ratio of 50 within 24 h was prospectively defined as improvement in our protocol. Our prior clinical experience with PCV and HFOV has shown this to be a useful clinical guideline. We did not explore the sensitivity of the criteria for improvement on a post hoc basis.

Only conflicting and limited data are reported in the literature on the effect of HFOV on hemodynamics in adults. Fort et al. [14] reported a brief but significant increase in mean pulmonary capillary wedge pressure (PCWP) although no change in mean pulmonary artery pressure and cardiac output during the first 72 h of HFOV. Mehta and colleagues [13] observed a significant increase in left and right ventricular filling pressures but reduced cardiac output. The MOAT trial [12] found a slightly but significantly higher PCWP in those receiving HFOV than in the conventionally treated patients; at the same time, mean airway pressure increased in the HFOV group.

However, the correlation between PCWP and left ventricular volume during continuously elevated mean airway pressures by more than 15 cmH$_2$O is known to be very poor, and measured PCWP may more often reflect intra-alveolar pressure [21]. The association between higher mean airway pressures and decreased cardiac output has been well investigated and has been shown to result from reduced left ventricular filling [22]. We found no significant changes in mean arterial pressure in our patients. We do not routinely insert pulmonary artery catheters in these patients and therefore have no cardiac output data. While there is a relationship between circulating blood volume, right ventricular function, and CDP, none of these studies has detailed fluid management in the patients, and therefore it is difficult to interpret the reported differences.

The incidence of complications associated with HFOV was low in the present study. The observed incidence of pneumothorax was less than 3% (1/42) and less than the rate (5.9% and 8.3%) reported by two other studies [13, 14]. There were no tracheal injuries or mucus impaction during HFOV. Four trauma patients with increased, and hence monitored, intracranial pressure showed no deterioration during HFOV treatment (pressure data not included in this publication).

Conclusion

The finding that mechanical ventilation affects outcome in patients with ARDS has increased the interest in lung protective strategies and techniques. Our results suggest that HFOV is an effective and safe mode of ventilation in patients with severe ARDS. We found that increasing CDP above the mean airway pressure recommended as upper limit for PCV improves oxygenation without worsening ventilation or hemodynamics. We report that a negative oxygenation response to HFOV within the first 24 h of treatment, as defined in the study protocol, and a conventional ventilation period of more than 3 days prior to HFOV treatment was associated with higher mortality. Further studies are warranted to confirm our findings.

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