

High-frequency oscillatory ventilation for adult respiratory distress syndrome—A pilot study

Peter Fort, MD; Christopher Farmer, MD; Jan Westerman, MD; Jay Johannigman, MD; William Beninati, MD; Steven Dolan, MD; Stephen Derdak, DO

Objective: To evaluate the safety and effectiveness of high-frequency oscillatory ventilation using a protocol designed to recruit and maintain optimal lung volume in patients with severe adult respiratory distress syndrome (ARDS).

Setting: Surgical and medical intensive care units in a tertiary care, military teaching hospital.

Design: A prospective, clinical study.

Patients: Seventeen patients, 17 yrs to 83 yrs of age, with severe ARDS (Lung Injury Score of 3.81 ± 0.23) failing inverse ratio mechanical conventional ventilation (P_{aO_2}/F_{iO_2} ratio of 68.6 ± 21.6 , peak inspiratory pressure of 54.3 ± 12.7 cm H₂O, positive end-expiratory pressure of 18.2 ± 6.9 cm H₂O).

Interventions: High-frequency oscillatory ventilation was instituted after varying periods of conventional ventilation (5.12 ± 4.3 days). We employed a lung volume recruitment strategy that consisted of incremental increases in mean airway pressure to achieve a P_{aO_2} of ≥ 60 torr (≥ 8.0 kPa), with an F_{iO_2} of ≤ 0.6 .

Measurements and Main Results: High-frequency oscillator ventilator settings (F_{iO_2} , mean airway pressure, pressure amplitude of oscillation [ΔP] frequency) and hemodynamic parameters (cardiac output, oxygen delivery [Do_2]), mean systemic and pulmonary arterial pressures, and the oxygenation index (oxygenation index = [$F_{iO_2} \times$ mean airway pressure $\times 100$]/ P_{aO_2}) were monitored during the transition to high-frequency oscillatory ventilation and throughout

the course of the high-frequency protocol. Thirteen patients demonstrated improved gas exchange and an overall improvement in P_{aO_2}/F_{iO_2} ratio ($p < .02$). Reductions in the oxygenation index ($p < .01$) and F_{iO_2} ($p < .02$) at 12, 24, and 48 hrs after starting high-frequency oscillatory ventilation were observed. No significant compromise in cardiac output or Do_2 was observed, despite a significant increase in mean airway pressure (31.2 ± 10.3 to 34.0 ± 6.7 cm H₂O, $p < .05$) on high-frequency oscillatory ventilation. The overall survival rate at 30 days was 47%. A greater number of pretreatment days on conventional ventilation ($p < .009$) and an entry oxygenation index of >47 (sensitivity 100%, specificity 100%) were associated with mortality.

Conclusions: High-frequency oscillatory ventilation is both safe and effective in adult patients with severe ARDS failing conventional ventilation. A lung volume recruitment strategy during high-frequency oscillatory ventilation produced improved gas exchange without a compromise in Do_2 . These results are encouraging and support the need for a prospective, randomized trial of algorithm-controlled conventional ventilation vs. high-frequency oscillatory ventilation for adults with severe ARDS. (Crit Care Med 1997; 25:937-947)

KEY WORDS: high-frequency ventilation; adult respiratory distress syndrome; high-frequency oscillation

Recent consensus conferences on mechanical ventilation in adult respiratory distress syndrome (ARDS) have recognized conventional mechanical ventilator therapy-induced lung injury as

a possible mechanism for failure of ARDS mortality to decrease during the past 15 to 20 yrs (1-6). Their guidelines for mechanical ventilatory support in patients with ARDS include recruitment of atelectatic alveoli and avoidance of lung trauma from overdistention of air spaces. These recommendations stem from the observation that the severe ARDS lung is non-uniformly injured and retains only a small fraction of compliant lung still capable of gas exchange. The application of conventional tidal volumes to this relatively small lung may cause, as demonstrated mostly in animal data, overdistention and damage to the remaining functional alveoli units (7-10). As such, alternative ventilatory modalities have been introduced to limit

alveoli overdistention. These modalities include intentional hypoventilation, with and without tracheal gas insufflation, and reduction of peak pressures permitted by pressure controlled inverse ratio ventilation or by low-frequency positive-pressure ventilation-extracorporeal CO₂ removal (11-15). However, there is no current proof that any of these modalities alter the outcome of patients with ARDS. High-frequency oscillatory ventilation may be one more way of achieving the consensus goals of reversing atelectasis while avoiding overdistention of alveoli in patients suffering from severe ARDS (16, 17). High-frequency oscillatory ventilation is characterized by achieving gas exchange utilizing subdead-space tidal volumes, and, as

From the Departments of Pulmonary/Critical Care Medicine and Surgery, Wilford Hall Medical Center, Lackland AFB, San Antonio, TX.

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Address requests for reprints to: Peter Fort, MD, Major, USAF, MC, WHMC/PSMP Central Distribution, 2200 Bergquist Drive, Suite 1, Wilford Hall Medical Center, Lackland AFB, TX 78236-5300.

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such, may provide a less traumatic method of recruiting and stabilizing lung volumes than other conventional and alternative modalities.

Animal data convincingly support the concept of reduced lung injury utilizing high-frequency oscillatory ventilation. Studies (18–20) in premature primates and surfactant-deficient adult rabbits demonstrate that when compared with conventional ventilation, high-frequency oscillatory ventilation can improve gas exchange, promote uniform lung inflation, reduce lung injury, and reduce the frequency rate of hyaline membrane disease. In addition, high-frequency oscillatory ventilation is associated with reduced inflammatory mediators and granulocytes in lung lavage samples when compared with conventional ventilation (19, 21, 22). Neonatal models (23–25) also have demonstrated that high-frequency oscillatory ventilation is most effective when it is used early in the course of lung injury in combination with exogenous surfactant. In surfactant-deficient adult rabbit models (25, 26), higher mean airway pressures and lung volumes are more effective at reducing lung injury than high-frequency oscillatory ventilation at low lung volumes. Thus, minimization of lung injury with high-frequency oscillatory ventilation appears to require maintenance of an adequate alveolar volume with an appropriate mean airway pressure that prevents derecruitment and atelectasis (27).

Despite compelling animal data (18–27) supporting the use of high-frequency ventilation in ARDS, early prospective, controlled, clinical trials (28–30) have been unable to demonstrate a superiority of high-frequency ventilation over conventional ventilation (28–30). In the largest controlled study (28) of high-frequency jet ventilation in adult ARDS, mean airway pressure on high-frequency jet ventilation was less than that pressure on conventional ventilation, and mortality may have been affected by the large percentage (60%) of patients with underlying malignancies. In a recent, uncontrolled trial (31) of high-frequency jet ventilation in adult ARDS, significant reductions in FiO_2 were demonstrated. Improved oxygenation was thought to occur by recruiting and maintaining lung volume at an equivalent

mean airway pressure as that of conventional ventilation and by utilizing a frequency of jet ventilation that more closely approximated the resonant frequency of the lung (31).

High-frequency oscillation has been primarily studied in children and neonates. The HIFI study group (29) failed to show any advantage in oxygenation or ventilator-associated complications in preterm infants receiving high-frequency oscillatory ventilation compared with those infants receiving conventional ventilation. However, in a study (32) using a higher mean airway pressure on high-frequency oscillatory ventilation than conventional ventilation, the HiFO study group (32) demonstrated improved gas exchange and a significant reduction in the development of the airleak syndrome in preterm infants receiving high-frequency ventilation. A similar volume recruitment strategy on high-frequency oscillatory ventilation was utilized in children with ARDS in a controlled, randomized, crossover protocol (33, 34) demonstrating significant improvements in oxygenation, reductions in barotrauma, and overall improved outcome in those children receiving high-frequency oscillatory ventilation or those children crossed over to receive high-frequency oscillatory ventilation.

The use of high-frequency oscillatory ventilation in adults with severe ARDS has not been studied, and although similar to high-frequency jet ventilation, may offer critical differences. A high-frequency oscillatory prototype ventilator (3100B, SensorMedics, Yorba Linda, CA) has been developed that utilizes an oscillating diaphragm, has both an active inspiratory and expiratory phase of ventilation, has an efficient humidification system incorporated into the bias flow, and does not require a specialized endotracheal tube.

The specific aim of this study was to evaluate the application and safety of a high-frequency oscillatory ventilator prototype in adult patients with severe ARDS failing conventional ventilation. As in recent high-frequency oscillatory ventilation trials in neonates and children with respiratory distress, we employed a lung recruitment strategy of ventilation that consisted of incremental increases in mean airway pressures

and lung volumes to achieve oxygenation targets.

MATERIALS AND METHODS

Design. We employed a prospective, uncontrolled trial of high-frequency oscillatory ventilation in adults with severe ARDS failing conventional ventilation.

Ventilator. The ventilator used was an adult high-frequency ventilator prototype (3100B, SensorMedics). This prototype ventilator, in order to accommodate the adult patient, differs from the 3100A model used in neonates and children in that it has a higher potential bias flow (≤ 90 L/min), a more powerful electromagnet allowing for a faster acceleration to pressure amplitude of oscillation (DP) and larger diameter patient circuit tubing.

Patient Selection. This study included patients from the medical and surgical intensive care units at Wilford Hall Medical Center, San Antonio, TX. The study protocol was approved by the Investigational Review Board. Surrogate consent from the family and the primary physician was obtained for all patients. Patients with ARDS who met the following entry criteria were considered eligible for ventilation with the prototype high-frequency oscillatory ventilator: a) age >18 yrs or body weight >35 kg; b) failing conventional ventilation, as defined by meeting any one of the following criteria—an FiO_2 of ≥ 0.7 with a PaO_2 of ≤ 65 torr (≤ 8.7 kPa), a peak inspiratory pressure of ≥ 65 cm H_2O , or a positive end-expiratory pressure (PEEP) of ≥ 15 cm H_2O ; c) ARDS Lung Injury Score of ≥ 2.5 (chest radiograph criteria included) (35); and d) pulmonary artery occlusion pressure (PAOP) of ≤ 18 mm Hg.

Patients were excluded from enrollment if they had the following: a) cardiogenic pulmonary edema, as defined by a cardiac index of ≤ 1.9 L/min/m² and a PAOP of ≥ 18 mm Hg; b) severe obstructive lung disease; c) intractable septic shock requiring >15 $\mu\text{g/kg/min}$ of dopamine or >4 $\mu\text{g/kg/min}$ of norepinephrine; or d) pregnancy.

Methodology. All patients were treated with conventional ventilation (7200ae, Puritan-Bennett, Overland, KS; 900c, Siemens Medical Systems, Iselin, NJ) before institution of high-frequency oscillatory ventilation.

Increases in PEEP, inspiratory time, and FIO_2 were employed to improve oxygenation on conventional ventilation. Before the institution of high-frequency ventilation, all patients were receiving either volume- or pressure-controlled inverse ratio ventilation, were paralyzed with either vecuronium or atracurium, and sedated with a combination of opioid and benzodiazepine.

All patients were maintained on their general supportive care, including paralysis and sedation, fluid maintenance, nutritional support, and antibiotics. Pulmonary artery catheters were placed to monitor the hemodynamic consequences of high-frequency oscillatory ventilation and arterial catheters were utilized for rapid arterial blood gas analysis.

Initial high-frequency oscillatory ventilation settings were as follows: a) FIO_2 of 1.0; b) frequency of 5 Hz; c) inspiratory time of 50%; d) bias flow of 30 L/min; e) mean airway pressure 2 to 3 cm H_2O above mean airway pressure setting on conventional ventilation; and f) ΔP setting based on Paco_2 (Table 1).

High-Frequency Oscillatory Ventilation Strategy. The target Paco_2 was between 35 and 60 torr (4.7 and 8.0 kPa), provided pH could be maintained above 7.25. Modulation of Paco_2 was accomplished by either varying ΔP (to a maximum of 90 cm H_2O) or changing oscillatory frequency (to a minimum of 3 Hz). The pressure amplitude of oscillation, or ΔP , is attenuated greatly by the endotracheal tube. According to specifications listed in the 3100B high-frequency oscillatory ventilator operator's manual (SensorMedics), given a 8.0-mm endotracheal tube and a frequency of 5 Hz, the distal ΔP is ~15% of the proximal ΔP .

Oxygenation Strategy. A volume recruitment strategy was affected by initially setting the mean airway pressure 2 to 3 cm H_2O above the mean airway pressure on conventional

ventilation. If oxygen saturation was $\geq 90\%$, then FIO_2 was reduced in steplike fashion to achieve a target FIO_2 of ≤ 0.6 . If oxygen saturation was $\leq 90\%$, then mean airway pressure was similarly increased by 1 to 2 cm H_2O to a maximum mean airway pressure of 45 cm H_2O , if necessary, provided no adverse effects on cardiac output or oxygen delivery ($\dot{\text{V}}\text{O}_2$) were observed.

Weaning/Withdrawal From High-Frequency Oscillatory Ventilation. Patients were withdrawn from high-frequency oscillatory ventilation when they were considered a protocol failure or suffered intractable hypotension unresponsive to adequate preload (e.g., a PAOP of ≥ 20 cm H_2O) or inotropic support. Patients whose Paco_2 remained >60 torr (>8.0 kPa) and pH ≤ 7.25 , despite maximal ΔP and minimum frequency, were considered a ventilatory failure. Patients unable to maintain an oxygen saturation of $\geq 90\%$, despite maximal mean airway pressure and FIO_2 , were considered an oxygenation failure. The weaning process was initiated once FIO_2 was ≤ 0.4 . Mean airway pressure was gradually decreased by 1 to 2 cm H_2O and transfer back to conventional ventilation occurred when mean airway pressure reached ~20 to 22 cm H_2O . Successful wean to conventional ventilation was defined as an oxygen saturation of $\geq 90\%$, with an FIO_2 of ≤ 0.4 and a mean airway pressure less than or equal to the mean airway pressure on high-frequency oscillatory ventilation.

Humidification/Tracheal Suctioning. The high-frequency oscillatory ventilator utilizes a humidifier placed in line with the bias flow circuit. Confirmation of adequate humidification was achieved visually by noting condensation along the inspiratory tubing. To exclude the possibility of subclinical tracheitis, bronchoscopy was performed on the first three patients enrolled. Tracheal suctioning was achieved by placing an in-line suction catheter (Steri-Cath 6100, 14-Fr, Smith Industries, Keene, NH) between the endotracheal tube and ventilator circuit. Since the catheter adapter induces a 90° connection between the ventilator and the patient's endotracheal tube, the suction catheter was only placed in line if adequate ventilation and oxygenation were demonstrated without the catheter adapter.

Patients were subsequently observed for deterioration in ventilation and oxygenation with the catheter adapter in place.

Data Collection. Hemodynamic parameters, ventilator settings, and gas exchange data were recorded just before initiating high-frequency oscillatory ventilation (baseline) and then at 0.5, 1.0, 2.0, 3.0, 6.0, 9.0, and 12.0 hrs. Subsequent measurements were recorded every 6 hrs for the first 48 hrs and additional parameters were obtained based on oxygen saturation values and clinical indications. Mean airway pressure, inspiratory time, ΔP , and frequency were recorded from the visual display on the high-frequency oscillatory ventilator. FIO_2 was measured using an in-line FIO_2 analyzer (5590, Hudson, Temecula, CA). Hemodynamic variables and thermodilution cardiac output values were recorded from a 7.5-Fr balloon pulmonary artery catheter and hemodynamic computer (Marquette Electronics, Milwaukee, WI). The oxygenation index was defined as follows: $([\text{mean airway pressure} \times \text{FIO}_2 \times 100] / \text{Pao}_2)$ (33). $\dot{\text{V}}\text{O}_2$ was determined from the equation: $\text{cardiac output} \times ([\text{hemoglobin} \times 1.36 \times \text{arterial O}_2 \text{ saturation}] + [\text{Pao}_2] / 0.003)$. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were computed at the start of high-frequency oscillatory ventilation (36). Survival at 30 days after initiating high-frequency oscillatory ventilation was recorded.

Statistics. We tested the null hypothesis that there was no change in gas exchange or hemodynamic parameters after initiating high-frequency oscillatory ventilation. A $p < .05$ was considered significant. Comparisons of measured variables over time in individuals was made by a two-tailed Wilcoxon matched-pairs test. Comparisons between entry characteristics of survivors and nonsurvivors were determined by a two-tailed Mann-Whitney U rank sum test. Spearman's correlation coefficient was used to determine correlations between entry minute ventilation and changes in Paco_2 at 3 hrs, and between entry oxygenation index and days on conventional ventilation before high-frequency oscillatory ventilation. Data are expressed as mean \pm sd. All calculations were performed by SPSS (SPSS for Windows, 6.1, SPSS Inc., Chicago, IL).

Table 1. Initial pressure amplitude of oscillation (ΔP) setting based on Paco_2

Paco_2 (torr)	ΔP (cm H_2O)
60	60
60-70	75
>70	90

To convert torr to kPa, multiply the value by 0.1333.

RESULTS

Severity of Illness. Seventeen patients (nine male), ranging in age from 16 to 83 yrs, were enrolled in the study protocol (Table 2). These patients were the first 17 patients placed on high-frequency oscillatory ventilation at our institution and their cause of ARDS included sepsis in six patients, pneumonia in five patients, trauma in three patients, aspiration in two patients, and rhabdomyolysis in one patient. Patients received conventional ventilation for 5.12 ± 4.3 days before high-frequency oscillatory ventilation. The same endotracheal tube or tracheostomy (average 7.75 ± 0.32 mm) was used for both conventional ventilation and high-frequency oscillatory ventilation. All patients had severe ARDS, as noted by an average Lung Injury Score of 3.81 ± 0.23 (35). Before initiation of high-frequency oscillatory ventilation, average values of PEEP, peak inspiratory pressure, mean airway pressure, and P_{aO_2}/F_{iO_2} ratio were 18.33 ± 7.32 cm H₂O, 54 ± 13.4 cm H₂O, 31.2 ± 10.7 cm H₂O, and 66.13 ± 19.01 , respectively. Notably, the mean oxygenation index was markedly increased (48.56 ± 15.17). The oxygenation index, an indicator of the mean airway pressure cost of oxygenation, is often used in neonatal and pediatric literature to

define lung injury and reduced lung compliance. An oxygenation index of >30 is generally accepted to represent failure of conventional ventilation or an indication for high-frequency ventilation or extracorporeal membrane oxygenation (ECMO) (32, 37, 38). The average APACHE II score was 23.3 ± 7.5 . According to APACHE II data, this score would translate to an overall nonoperative hospital mortality rate of 40%. However, in the setting of respiratory failure from infection or sepsis, a 50% to 60% hospital mortality rate would be expected (36).

Ventilator Response. Table 3 lists the changes in high-frequency oscillatory ventilation settings. As per protocol design, the mean airway pressure significantly increased initially (3 hrs) to achieve volume recruitment. Significant reductions in F_{iO_2} were observed as early as 3 hrs after initiating high-frequency oscillatory ventilation and continued to decrease throughout the 48-hr period without hemodynamic compromise. As the patients' oxygenation requirements improved, a trend toward decreasing mean airway pressure was observed. ΔP , the pressure amplitude of oscillation and a determinant of delivered tidal volume, showed a slight upward trend to achieve target ventilation. Likewise, as lower oscillatory frequencies increase diaphragm

excursion and tidal volume, a trend toward slightly lower frequencies was observed at 12 hrs. The bias flow was maintained at 30 to 40 L/min, unless an increase was required to increase mean airway pressure.

Gas Exchange. Figure 1 demonstrates changes in the P_{aO_2}/F_{iO_2} ratio and oxygenation index. Before high-frequency oscillatory ventilation, the oxygenation index increased and the P_{aO_2}/F_{iO_2} ratio remained severely low. This finding indicates a worsening degree of oxygenation efficiency in that higher mean airway pressure was required to achieve a stable gas exchange before high-frequency oscillatory ventilation. Initiation of high-frequency oscillatory ventilation caused significant increases in P_{aO_2}/F_{iO_2} ratio, as early as 3 hrs, and significant reductions in the oxygenation index at 12 hrs. Overall, target ventilation was easily achieved with the high-frequency oscillatory ventilator over a broad range of minute ventilation, although there was a significant correlation toward a higher P_{aCO_2} in patients with higher ventilatory requirements (Fig. 2).

Hemodynamic Changes. Table 4 lists changes in the hemodynamic variables on high-frequency oscillatory ventilation. As a group, initiation and maintenance of high-frequency oscillatory ventilation did not induce any signifi-

Table 2. Patient characteristics

Pt.	Age (yr)	Gender (M/F)	LIS	APACHE II	Diagnosis	ETT (mm)	PIP (cm H ₂ O)	PEEP (cm H ₂ O)	Days	Outcome
1	50	F	3.75	15	Sepsis	7.0	53	10	1	S
2	48	M	3.50	18	Aspiration	8.0	54	15	1	S
3	22	M	4.00		Rhabdomyolysis	8.0	70	20	7	D
4	57	F	4.00	26	IPF/pneumonia	8.0	64	20	2	D
5	16	F	3.75	21	Sepsis	7.5	57	12	4	D
6	18	F	4.00	12	Sepsis	7.5	60	22	1	S
7	40	F	4.00	21	Pneumonia	8.0	88	34	15	D
8	21	M	3.75		Pneumonia	8.0	44	18	9	D
9	17	M	4.00		Trauma	8.0	55	20	2	D
10	48	F	3.50	29	Sepsis	7.5	57	10	9	S
11	17	M	4.00	41	Trauma	Trach (6)	59	20	12	D
12	30	M	3.25	24	Sepsis	7.5	35	7	1	S
13	83	F	4.00	31	Aspiration	7.5	46	30	6	D
14	17	F	4.00	18	Trauma	7.5	47	22	2	S
15	58	M	3.75	23	Pneumonia	8.0	52	20	8	D
16	65	M	3.75		Pneumonia	8.0	35	15	2	S
17	39	M	3.75	24	Sepsis	8.0	47	15	5	S
Mean	38.00		3.81	23.31		7.75	54.29	18.24	5.12	
± SD	± 20.43		± 0.23	± 7.51		± 0.32	± 12.70	± 6.91	± 4.30	

Pt., patient; LIS, Lung Injury Score (Shanholtz and Brower [13]); APACHE II, Acute Physiology and Chronic Health Evaluation II score (Knaus et al. [36]); ETT, endotracheal tube size; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; Days, number of days on conventional ventilation before high-frequency oscillatory ventilation; S, survived; D, died; IPF, interstitial pulmonary fibrosis; Trach, tracheostomy.

Table 3. Changes in ventilator settings on high-frequency oscillatory ventilation (HFOV) (mean \pm SD)

	0 Hr	3 Hrs	12 Hrs	24 Hrs	48 Hrs
Paw (cm H ₂ O)	31.2 \pm 10.3	34.0 \pm 6.7 ^a	33.7 \pm 7.3	31.3 \pm 6.0	28.4 \pm 6.2
Δ P (cm H ₂ O)	67.0 \pm 13.1	72.3 \pm 15.8 ^a	72.5 \pm 16.8 ^a	68.7 \pm 16.3 ^a	65.1 \pm 19.6
Frequency (Hz)	5.2 \pm 1.3	4.8 \pm 1.6	4.8 \pm 1.7	4.9 \pm 1.9	5.2 \pm 1.9
F _I O ₂	0.94 \pm 0.10	0.72 \pm 0.21 ^b	0.57 \pm 0.17 ^b	0.51 \pm 0.09 ^b	0.47 \pm 0.09 ^b
Bias flow (L/min)	38.3 \pm 10.7	40.4 \pm 14.5	44.2 \pm 16.5	39.5 \pm 10.6	35.6 \pm 8.2

Paw, mean airway pressure; Δ P, pressure amplitude of oscillation.

^a*p* < .05; ^b*p* < .02.

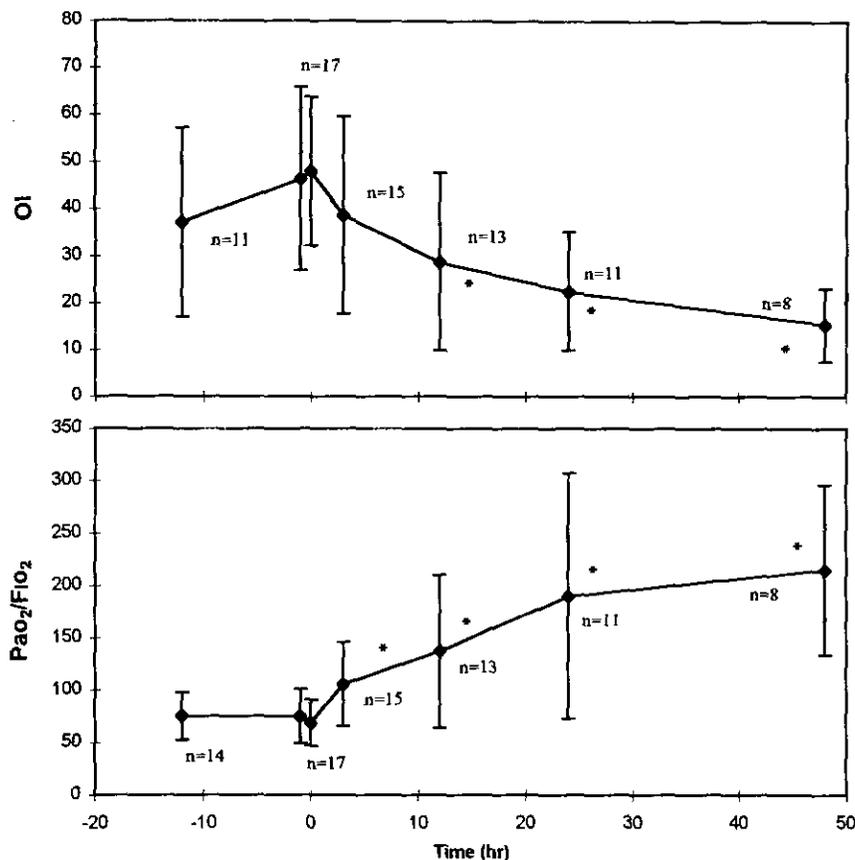


Figure 1. Time course of changes in oxygenation index (OI; top) and PaO₂/F_IO₂ ratio (bottom) after initiation of high-frequency oscillatory ventilation. High-frequency oscillatory ventilation was instituted at hour 0, which represents the last conventional ventilatory setting before beginning the protocol. Values are mean \pm SD. **p* < .01, compared with hour 0.

cant improvement or detriment in any of the hemodynamic variables, such as cardiac output, $\dot{V}O_2$, or mean arterial pressure. PAOP increased significantly at 3 and 12 hrs, and then showed a downward trend over the next 36 hrs, possibly reflecting similar changes in the mean airway pressure.

Weaning/Withdrawal. Table 5 clarifies when patients were withdrawn to receive conventional ventilation. Essentially, all patients were eventually withdrawn to receive conventional ventilation for the following reasons:

Met Weaning Criteria. Eight patients were withdrawn due to improved oxygenation and because they met weaning criteria, i.e., F_IO₂ was <4.0 and mean airway pressure was <22 cm H₂O. Of these eight patients, seven patients were survivors, and the other patient died of multiple system organ failure (nonrespiratory) 10 days after being withdrawn to receive conventional ventilation.

Oxygenation/Ventilation Failures. Three patients were considered oxygenation failures with high-frequency

oscillatory ventilation. Two patients had stable oxygenation status but failed to improve their oxygenation, or PaO₂/F_IO₂ ratio, at 5 and 12 hrs of high-frequency oscillatory ventilation, despite use of maximal settings on high-frequency oscillatory ventilation (i.e., mean airway pressure of 45 cm H₂O, 50% inspiratory time). One patient developed worsening oxygenation on high-frequency oscillation, despite use of maximal settings, and was withdrawn to receive conventional ventilation at 1.5 hrs. All other patients demonstrated improved PaO₂/F_IO₂ ratio on high-frequency oscillatory ventilation, regardless of their outcome. Only one patient was considered a ventilation failure, with a PaCO₂ increasing from 40 to 72 torr (5.3 to 9.6 kPa) at 4 hrs despite maximal settings on high-frequency oscillatory ventilation (Δ P of 90 cm H₂O, and frequency of 3 Hz). This patient was discovered to have mucous inspissated secretions causing narrowing of the inner diameter of the endotracheal tube. The reduced diameter of the endotracheal tube was thought to have significantly attenuated the oscillatory waveform. Thus, it is possible that given a more patent endotracheal tube, this patient would not have been a ventilatory failure. We subsequently believe it is important to do a bronchoscopy to check for airway patency before high-frequency oscillatory ventilation is begun in patients who have been on prolonged mechanical ventilation. All patients who had oxygenation failures died, two patients of respiratory failure and one patient of multiple system organ failure. The patient who was a ventilation failure survived on conventional ventilation and after undergoing a tracheostomy.

Hypotension. Three patients were withdrawn due to hypotension. Two of these patients had improved oxygenation on high-frequency oscillatory ventilation at 5 days and 1 day but had not yet met weaning criteria, and the other patient had no improvement in oxygenation at 3 hrs. Hypotension was caused by high-frequency oscillatory ventilation in two patients and by post-operative bleeding in the other patient. All three patients died, two patients from multiple system organ failure and one patient from respiratory failure.

Withdrawal of Care. One patient who had sustained a severe head injury demonstrated improved oxygen-

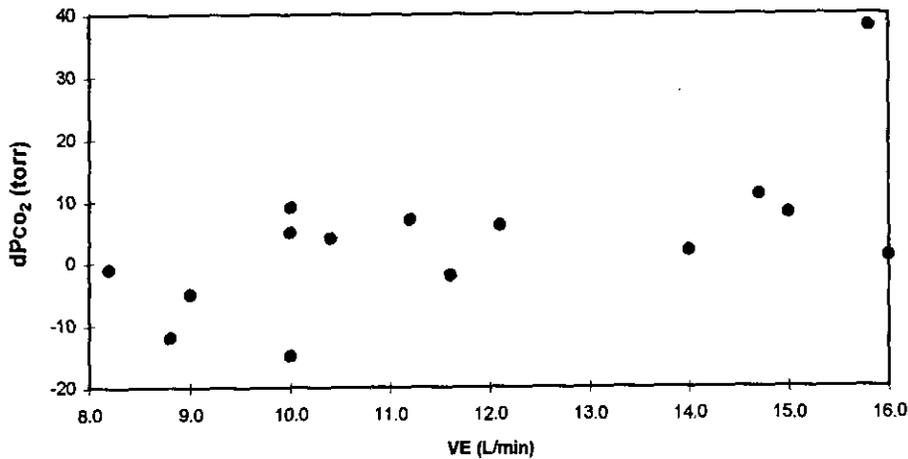


Figure 2. Entry minute ventilation (VE) plotted against the change in arterial partial pressure of CO₂ (dPco₂) at 3 hrs after instituting high-frequency oscillatory ventilation. Entry minute ventilation significantly correlated with dPco₂ ($r^2 = .30$, $p < .033$).

Table 4. Changes in hemodynamic variables on high-frequency oscillatory ventilation (HFOV) (mean \pm SD)

	0 Hr (n = 17)	3 Hrs (n = 15)	12 Hrs (n = 13)	24 Hrs (n = 11)	48 Hrs (n = 8)
CO (L/min)	6.95 \pm 3.4	7.0 \pm 2.0	6.9 \pm 1.6	6.6 \pm 2.0	6.4 \pm 1.7
Do ₂ (L O ₂ /min)	1.01 \pm 0.55	1.04 \pm 0.34	1.05 \pm 0.28	0.97 \pm 0.33	1.00 \pm 0.35
Heart rate (beats/min)	114 \pm 20	114 \pm 22	108 \pm 21	110 \pm 24	102 \pm 12
MPAP (mm Hg)	35.3 \pm 8.4	36.4 \pm 6.7	35.9 \pm 7.1	33.6 \pm 6.8	32.1 \pm 7.4
MAP (mm Hg)	75.3 \pm 16.4	75.7 \pm 14.5	78.8 \pm 18.1	85.3 \pm 21.2	88.2 \pm 14.7
PAOP (mm Hg)	18.4 \pm 5.7	20.5 \pm 5.09*	21.1 \pm 5.0*	19.9 \pm 5.9	16.8 \pm 2.7

CO, cardiac output; Do₂, oxygen delivery; MPAP, mean pulmonary arterial pressure; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure.

* $p < .05$.

ation on high-frequency oscillatory ventilation but had not yet met weaning criteria at 2 days of high-frequency oscillatory ventilation. Due to the patient's neurologic prognoses, a do-not-resuscitate order was initiated and care was withdrawn at the family's request.

Equipment Failure. One patient, patient 3, demonstrated improved oxygenation on high-frequency oscillatory ventilation at 7 hrs. The patient, however, had not yet met weaning criteria, and was withdrawn from high-frequency oscillatory ventilation due to a sudden increase in mean airway pressure associated with an electrical smell emanating from the ventilator. An overheated electromagnet was discovered as the cause of this malfunction and an improved cooling system was installed on the high-frequency oscillator. The patient died of multiple system organ failure 4 days after withdrawing from high-frequency oscillatory ventilation. No subsequent cases

of equipment malfunction were noted in this series.

Complications. One patient who developed bilateral pneumothoraces on high-frequency oscillatory ventilation had evidence of a pneumomediastinum before high-frequency oscillatory ventilation. One patient had bilateral bronchopleural fistulas before high-frequency oscillatory ventilation. High-frequency oscillatory ventilation did not cause worsening barotrauma in this patient. Three patients developed hypotension as noted above. No significant tracheitis was observed via bronchoscopy in the three initial high-frequency oscillatory ventilation patients, and subsequent patients were observed clinically for evidence of tracheitis. Mucous inspissation causing narrowing of the inner diameter of the endotracheal tube was observed in one patient. However, since the patient had only been receiving high-frequency oscillatory ventilation for a few hours, it was doubtful that this inspissation

occurred as a result of high-frequency oscillatory ventilation. The addition of a catheter adapter between the endotracheal tube and the high-frequency oscillatory ventilation tubing did not cause any detriment to oxygenation and ventilation.

Survivors vs. Nonsurvivors. At 30 days, eight (47%) of 17 patients were alive. Of the nine nonsurvivors, four patients were considered an oxygenation/ventilation failure. Five patients who had improved gas exchange on high-frequency oscillatory ventilation nevertheless died of nonrespiratory causes (i.e., bleeding [n = 1], multiple system organ failure [n = 4]). Thus, the mortality rate due to respiratory-related factors was 33%.

Figure 3 demonstrates changes in the PaO₂/Fio₂ ratio and oxygenation index over time in both survivors and nonsurvivors. The survivors had significant increases in the PaO₂/Fio₂ ratio and decreases in the oxygenation index over time. No significant changes were noted in nonsurvivors. Although survivors and nonsurvivors had similar PaO₂/Fio₂ ratios at the start of high-frequency oscillatory ventilation, nonsurvivors had significantly higher oxygenation indices, or pressure cost of oxygenation. Of the nine nonsurvivors, five patients showed improvement in gas exchange and reduction in the oxygenation index. In contrast, seven of eight survivors demonstrated improved gas exchange and reduced oxygenation index on high-frequency oscillatory ventilation.

Table 6 lists a comparison of initial characteristics between survivors and nonsurvivors before initiating high-frequency oscillatory ventilation. The nonsurvivors had significantly more days on conventional ventilation before high-frequency oscillatory ventilation. In addition, nonsurvivors could be characterized by higher Lung Injury Scores, higher oxygenation indices, and they required higher levels of PEEP than the survivors. The APACHE II scores also tended to be greater in the nonsurvivors. The most significant discriminating characteristic between survivors and nonsurvivors was the oxygenation index ($p < .0012$). Nonsurvivors had a range of oxygenation index before high-frequency oscillatory ventilation of between 48 and 71, compared with survivors, whose oxygenation index ranged between 22

Table 5. Patient outcomes on high-frequency oscillatory ventilation (HFOV)

Pt.	Days on CV	Duration of HFOV	Reason for Withdrawal to CV	Complications of HFOV	Outcome
1	1	4 days	Met weaning criteria	None	Survived, no respiratory support
2	1	2 days	Met weaning criteria	None	Survived, no respiratory support
3	2	7 hrs	Equipment failure—overheated electric unit	Transient increase in P_{aw} associated with equipment malfunction	Died of MSOF 4 days after withdrawing to CV. Improved oxygenation on HFOV that persisted on CV
4	2	6 days	Met weaning criteria	None	Died of MSOF 10 days after withdrawing to CV
5	4	5 days	Hypotension	Bilateral pneumothoraces. Had pneumomediastinum prior to HFOV	Died of MSOF several hours after withdrawing to CV. Improved oxygenation on HFOV
6	1	1.5 days	Met weaning criteria	None	Survived. No respiratory support
7	15	12 hrs	Failure to improve oxygenation despite maximum settings on HFOV	None	Died of Respiratory failure/MSOF 5 days after withdrawing to CV
8	9	5 hrs	Failure to improve oxygenation despite maximum settings on HFOV	None	Died of MSOF/sepsis hours after withdrawing to CV
9	7	1 day	Hypotension	None—cause of hypotension related to postoperative bleeding	Died of EMD from complications of surgery. Improved oxygenation on HFOV
10	2	3 days	Met weaning criteria	None	Survived. Ventilator dependence
11	12	2 days	Withdrawal of care	None	Died of MSOF/withdrawal of care. Status post severe head injury. Improved oxygenation and ventilation on HFOV
12	1	3 days	Met weaning criteria	None	Survived. No respiratory support
13	6	3 hrs	Hypotension. No improvement in oxygenation	Hypotension. Required maximum vasopressor support	Died of respiratory failure
14	7	5 days	Met weaning criteria	None	Survived. Ventilatory support (trach collar 35% F_{iO_2})
15	8	1.5 hrs	Worsening oxygenation and ventilation on HFOV	None	Died of respiratory failure
16	2	2 days	Met weaning criteria	None	Survived. Ventilatory support (face tent 40% F_{iO_2})
17	5	4 hrs	Worsening ventilation	Mucous inspissation causing narrowing of ETT	Survived. Ventilatory support (trach collar 35%)

Pt., patient; CV, conventional ventilation; P_{aw} , mean airway pressure; MSOF, multiple system organ failure; EMD, electromechanical dissociation; Trach, tracheostomy; ETT, endotracheal tube.

and 46. An oxygenation index of >47 predicted mortality (sensitivity 100%, specificity 100%). Figure 4 demonstrates a significant correlation between initial oxygenation index and number of pretreatment days on conventional ventilation ($r^2 = .28, p < .029$). A greater number of pretreatment days on conventional ventilation was associated with an increased oxygenation index, i.e., >50 , and adverse outcome.

DISCUSSION

The results of this study indicate that high-frequency oscillatory ventilation significantly improved gas

exchange and reduced F_{iO_2} requirements in patients with severe ARDS (satisfying ECMO criteria). In contrast, in the largest, randomized, controlled study (28) to date, high-frequency jet ventilation was effective but no better than conventional ventilation in maintaining ventilation and oxygenation in patients with ARDS. Patient selection (60% malignancies) and a low airway pressure strategy on high-frequency jet ventilation may have accounted for reduced efficacy with this technique (39). In an uncontrolled, multicenter trial (31) of high-frequency jet ventilation in adults with severe ARDS utilizing higher respiratory frequencies (>3 Hz)

that enables ventilation at the resonant frequencies of the lung and results in a virtually constant peripheral airway pressure, significant reductions in F_{iO_2} requirements (0.9 to 0.6 at 48 hrs) were demonstrated. Although peak inspiratory pressures were reduced, improved gas exchange was thought to occur by an overall increase in intra-alveolar pressure. Most recent trials (32–34) of high-frequency oscillatory ventilation in neonates and children with ARDS using a similar strategy of increasing intra-alveolar pressure and volume recruitment have also demonstrated improvements in gas exchange. Although gas exchange is readily

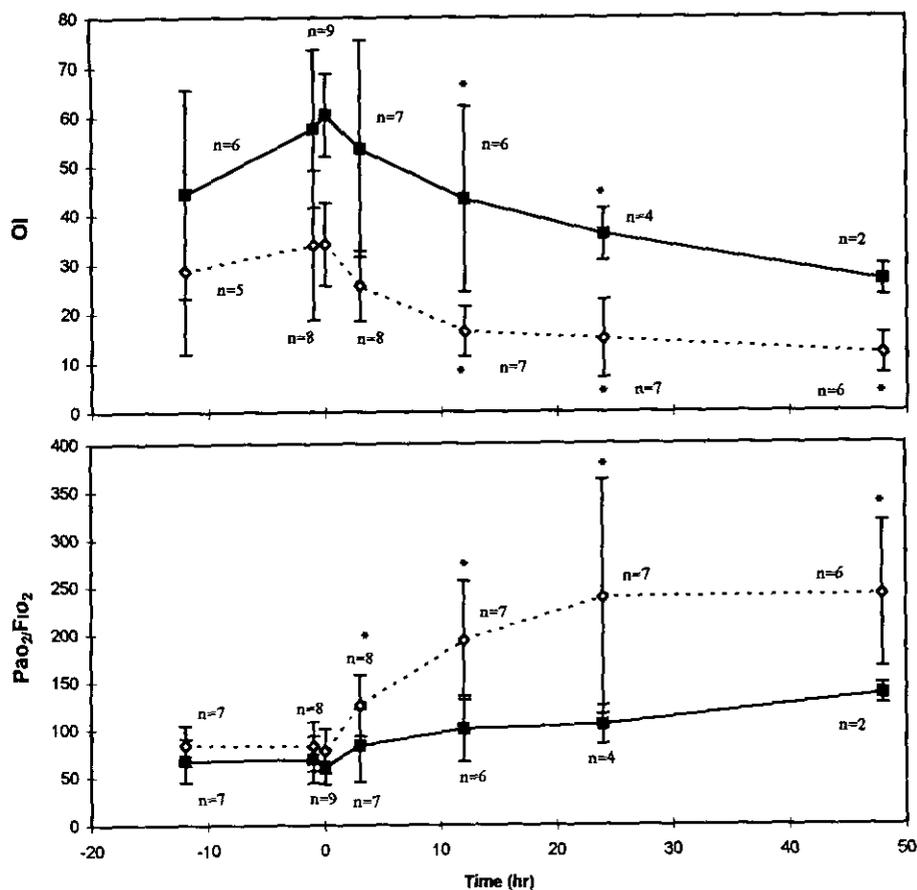


Figure 3. Time course of changes in the oxygenation index (*OI*; top) and P_{aO_2}/F_{iO_2} ratio (bottom) after initiation of high-frequency oscillatory ventilation in both survivors (solid squares) and nonsurvivors (open diamonds). High-frequency oscillatory ventilation was instituted at hour 0, which represents the last conventional ventilatory setting before beginning the protocol. Values are mean \pm SD. * $p < .02$, compared with hour 0.

Table 6. Baseline characteristics of survivors and nonsurvivors prior to high-frequency oscillatory ventilation (mean \pm SD)

	Survivors (n = 8)	Nonsurvivors (n = 9)	p Value
Days on CV	2.50 \pm 2.27	7.22 \pm 4.38	.009
LIS	3.69 \pm 0.26	3.92 \pm 0.13	.042
APACHE II	20.0 \pm 6.2	27.17 \pm 8.4	.11
OI (cm H ₂ O/mm Hg)	34.0 \pm 8.4	60.0 \pm 8.8	.0012
PEEP (cm H ₂ O)	14.4 \pm 5.9	21.7 \pm 6.9	.06
P_{aO_2}/F_{iO_2} (torr)	77.5 \pm 22.9	60.7 \pm 18.1	.048
P_{aCO_2} (torr)	38.9 \pm 11.5	49.9 \pm 11.6	.092

Days on CV, number of days on conventional ventilation before high-frequency oscillatory ventilation; LIS, Lung Injury Score (Murray et al. [35]); APACHE II, Acute Physiology and Chronic Health Evaluation II (Knaus et al. [36]); OI, oxygenation index; PEEP, positive end-expiratory pressure.

To convert torr to kPa, multiply the value by 0.1333.

achieved with high-frequency oscillatory ventilation from a variety of mechanisms, e.g., altered alveolar time constants, Taylor dispersion, bulk convection, and asymmetric velocity

profiles (17, 40), we believe the improvement in gas exchange in severe ARDS is predominately a result of a deliberate strategy of alveolar recruitment and maintenance of optimal lung

volume. It is unclear whether the patients in our series may have been sensitive to increases in mean airway pressure, of similar magnitude as on high-frequency oscillatory ventilation, during conventional ventilation. Until a prospective, randomized trial of algorithm-controlled ventilation vs. high-frequency oscillatory ventilation for adults with severe ARDS is completed, this question will remain unanswered. However, we believe the pre-high-frequency oscillatory ventilation data in Figures 1 and 3 suggest that patients will not respond to increases in mean airway pressure during conventional ventilation as they do on high-frequency oscillatory ventilation. On conventional ventilation, before placing our patients on high-frequency oscillatory ventilation, the mean airway pressure was increased, as demonstrated by an increasing oxygenation index, without significant improvements in gas exchange. In addition, the mean airway pressure, PEEP, and peak inspiratory pressure for the group just before high-frequency oscillatory ventilation was 29 to 30 cm H₂O, 17 cm H₂O, and 47 cm H₂O, respectively, demonstrating that conventional ventilatory settings were near maximal and further increases in mean airway pressure would require higher PEEP and peak inspiratory settings that may be deleterious. High-frequency oscillatory ventilation, on the other hand, allows ventilation to occur at much smaller tidal volumes. High-frequency oscillatory ventilation extends our options for volume recruitment well beyond those options attainable with conventional ventilation, inasmuch as mean airway pressure greater than those pressures usually tolerated on conventional ventilation can be used without exposing the lung to high peak pressures.

The survival rate for our population was 47%. Of those patients who died, 33% died due to progressive pulmonary insufficiency. In contrast, the ECMO trial (41) of 1974 to 1977 demonstrated an overall survival rate of 9% for similar patients randomized to receive both conventional ventilation and ECMO. Progressive pulmonary failure was the most common (>80%) cause of death. However, recent uncontrolled trials (42, 43) of low-frequency positive-pressure ventilation-extracorporeal CO₂ removal in severe ARDS have demonstrated

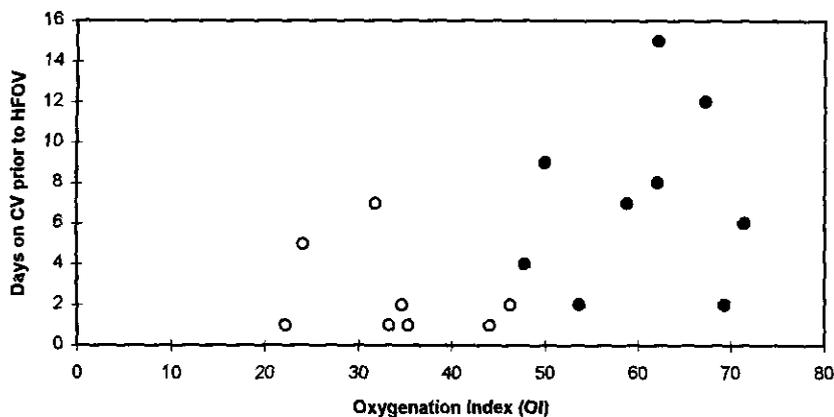


Figure 4. Entry oxygenation indices (OI) plotted against the number of pretreatment days on conventional ventilation (CV) prior to high-frequency oscillatory ventilation (HFOV) in survivors (open circles) and nonsurvivors (solid circles). Entry OI significantly correlated with days on conventional ventilation ($r^2 = .28$, $p < .029$).

improved survival rates of 48.8% and 50%. A subsequent study (15) of severe ARDS patients randomized to receive either conventional ventilation or pressure-controlled inverse ratio ventilation with extracorporeal CO₂ removal demonstrated an overall survival rate of 38% and no significant differences in survival between either group. Computerized protocols for management of arterial oxygenation to assure equivalent intensity of care of patients for both the control and new therapy groups may have accounted for the relatively low mortality. Despite entry characteristics, i.e., Pao₂/Fio₂ ratios, APACHE II scores, peak inspiratory pressures, and PEEP similar to our patients, a higher frequency of respiratory-related deaths (80%) was reported (15). Thus, survival with high-frequency oscillatory ventilation in severe ARDS in this study is comparable with historical controls and a reduction in respiratory-related deaths may be suggested. The increase in the survival rate on conventional ventilation, from 9% to 42%, between the ECMO trial of 1974 to 1977 and pressure controlled inverse ratio ventilation-extracorporeal CO₂ removal demonstrates the limitations of historical control subjects. A randomized, controlled trial of high-frequency oscillatory ventilation in severe ARDS is warranted for proper determination of survival data.

Reduced respiratory-related deaths using high-frequency oscillatory ventilation may be related to a reduction in lung injury with this method. We employed a ventilation strategy designed to rapidly recruit and maintain opti-

mal lung volume by incremental increases in mean airway pressure (44). Such "high volume" oscillatory strategy produces less phasic changes in alveolar pressure and volume than conventional ventilation. This hypothesis is supported by previous animal data (18-26) and randomized, controlled trials of high-frequency oscillatory ventilation in neonates and children (32-34) that showed reductions in airleak scores and requirements for supplemental oxygen at 30 days compared with conventional ventilation. In these studies (32-34), early intervention reduces the progression of lung injury. Likewise, we demonstrated that survivors had significantly fewer pretreatment days on conventional ventilation than nonsurvivors, suggesting that high-frequency oscillatory ventilation should be used earlier in the course of ARDS to reduce the possible risk of ventilator-associated lung injury.

To our knowledge, this is the first study of ARDS in adults reporting the oxygenation index. The oxygenation index has been used primarily in neonatal literature as a marker of lung compliance and the "mean airway pressure cost" of oxygenation. Because it assesses gas exchange as it relates to lung compliance, the oxygenation index may be a better indicator of ARDS severity than indices based only on various oxygen tensions. In the study of high-frequency oscillatory ventilation in children, pretreatment age and the oxygenation index were the two variables that predicted survival independently (34). An oxygenation index of >42 at 24 hrs predicted mortality (sensitivity 62%, specificity 93%). In addition,

an increasing oxygenation index over time significantly predicted adverse outcome compared with a decreasing oxygenation index over time. Similarly in this study, the pretreatment oxygenation index was the most significant variable that distinguished survivors from nonsurvivors. An oxygenation index of >47 predicted mortality (sensitivity 100%, specificity 100%). Only five of nine patients with a pretreatment oxygenation index of >47, compared with seven of eight patients with a pretreatment oxygenation index of <47, had improved gas exchange on high-frequency oscillatory ventilation. In addition, an increased pretreatment oxygenation index correlated with more days on conventional ventilation before high-frequency oscillatory ventilation. These data suggest that the oxygenation index is a potentially accurate tool to assess pulmonary insufficiency and mortality in ARDS. High-frequency oscillatory ventilation may be more effective at a lower pretreatment oxygenation index, i.e., <50, and after fewer days on conventional ventilation.

We employed a protocol designed to increase mean airway pressure for improved oxygenation and lung volume recruitment. Despite this strategy we demonstrated no significant adverse effects on cardiac output, blood pressure, or Do₂. Likewise, using a similar strategy of high-frequency oscillatory ventilation, previous studies (9, 13, 14) have also demonstrated stable hemodynamics. Although the use of high mean airway pressures in a normally compliant lung may cause overinflation and reduced cardiac output, transfer of airway pressures to intrapleural structures in a relatively noncompliant lung may be limited. We observed a trend toward improved mean arterial pressure and reduced mean pulmonary pressures, although this trend was not statistically significant as a group. This trend may reflect a reduction in pulmonary vascular resistance associated with lung volume recruitment (45). Thus, careful increases in mean airway pressure toward lung volume recruitment may have a beneficial, rather than adverse, effect on hemodynamics.

Initial studies (46, 47) of high-frequency oscillators in large animals (>30 kg) demonstrated inadequate alveolar ventilation, presumably due to an underpowered oscillator and low bias flow systems. To overcome these

We demonstrated that high-frequency oscillatory ventilation is both safe and effective in adult patients with severe ARDS failing conventional ventilation.

limitations, the SensorMedics 3100B was adapted from the neonatal and pediatric version and was equipped with a more powerful electromagnetically driven oscillator, increased bias flow, and a larger ventilator circuit. We found that alveolar ventilation was readily achieved over a broad range of initial minute ventilation with adjustments in ΔP and oscillatory frequency. Only one patient was withdrawn to receive conventional ventilation due to ventilatory failure associated with mucous inspersion and a narrowed endotracheal tube.

In summary, we demonstrated that high-frequency oscillatory ventilation is both safe and effective in adult patients with severe ARDS failing conventional ventilation. In this population, high-frequency oscillatory ventilation significantly improved oxygenation and reduced the mean airway pressure cost of oxygenation. An overall survival rate of 47% is consistent with prior studies in similar patients. We believe our results are encouraging and support the need for a prospective, randomized trial of algorithm-controlled conventional ventilation vs. high-frequency oscillatory ventilation for adults with severe ARDS. In addition to survival, other surrogate markers of efficacy should include frequency of barotrauma and chronic pulmonary insufficiency. Until such studies are completed, the use of high-frequency oscillatory ventilation for adults should be viewed as investigational.

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