High-Frequency Oscillatory Ventilation for Acute Respiratory Distress Syndrome in Adults

A Randomized, Controlled Trial

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Observational studies of high-frequency oscillatory ventilation in adults with the acute respiratory distress syndrome have demonstrated improvements in oxygenation. We designed a multicenter, randomized, controlled trial comparing the safety and effectiveness of high-frequency oscillatory ventilation with conventional ventilation in adults with acute respiratory distress syndrome; 148 adults with acute respiratory distress syndrome (Pa_{O_2}/fraction of inspired oxygen $\leq$ 200 mm Hg on 10 or more cm H_2O positive end-expiratory pressure) were randomized to high-frequency oscillatory ventilation (n = 75) or conventional ventilation (n = 73). Applied mean airway pressure was significantly higher in the high-frequency oscillation group compared with the conventional ventilation group throughout the first 72 hours (p = 0.0001). The high-frequency oscillation group showed early (less than 16 hours) improvement in Pa_{O_2}/fraction of inspired oxygen compared with the conventional ventilation group (p = 0.008); however, this difference did not persist beyond 24 hours. Oxygenation index decreased similarly over the first 72 hours in both groups. Thirty-day mortality was 37% in the high-frequency oscillation group and was 52% in the conventional ventilation group (p = 0.102). The percentage of patients alive without mechanical ventilation at Day 30 was 36% and 31% in the high-frequency oscillation and conventional ventilation groups, respectively (p = 0.686). There were no significant differences in hemodynamic variables, oxygenation failure, ventilation failure, barotraumas, or mucus plugging between treatment groups. We conclude that high-frequency oscillation is a safe and effective mode of ventilation for the treatment of acute respiratory distress syndrome in adults.

Keywords: acute respiratory distress syndrome; high-frequency ventilation; high-frequency oscillation; mechanical ventilation; oxygenation index

Mechanical ventilation may lead to further lung injury and may contribute to the systemic inflammatory response in patients with the acute respiratory distress syndrome (ARDS) (1–3). To avoid ventilator-induced lung injury, current recommendations focus on the avoidance of both alveolar overdistension and cyclic alveolar collapse and re-expansion, as well as achieving and maintaining alveolar recruitment (4–6). A recently published trial by the National Institutes of Health ARDS Network comparing a "lung protective" strategy of lower tidal volumes (6 ml/kg) and plateau pressures (less than 30 cm H_2O) with a higher tidal volume strategy found an absolute mortality reduction of 9% (7). This trial primarily targeted the avoidance of lung overdistension.

High-frequency oscillatory ventilation (HFOV) is a method of ventilation that theoretically achieves all of the goals of lung protective ventilation (6, 8). HFOV oscillates the lung around a constant mean airway pressure (mPaw) that is higher than that usually applied during conventional ventilation (CV). Although the oscillations may cause significant pressure swings in the endotracheal tube, the pressure fluctuations are significantly attenuated at the alveolar level (9–12). Distal attenuation of pressure swings depends on multiple variables, including endotracheal tube diameter, respiratory frequency, inspiratory time, lung compliance, and lung region (e.g., middle versus upper lobe). Application of a constant mPaw during HFOV allows maintenance of alveolar recruitment while avoiding low end-expiratory pressure and high peak pressures. The mechanisms of gas exchange during HFOV have previously been described (13, 14).

In premature primates and surfactant-deficient adult rabbits, the use of HFOV is associated with improved gas exchange, more uniform lung inflation, and reduced histopathologic evidence of ventilator-induced lung injury (15–17). Additionally, HFOV has been demonstrated to reduce levels of inflammatory mediators when compared with CV techniques applying similar mPaw values (18–20). In view of the encouraging findings with HFOV in animal models, numerous randomized clinical trials have been undertaken in neonatal and pediatric patients (21–24). None of these trials have shown a significant improvement in mortality. However, some of these studies have shown that HFOV, using a volume recruitment strategy, results in significant improvements in oxygenation without increasing barotrauma.

Published experience with HFOV in adults is limited to observational studies and case reports evaluating its use in patients failing CV (25–30). These studies report significant improvements in oxygenation using an open lung strategy, and a suggestion of better outcome when HFOV is applied early in the course of ARDS.

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TABLE 1. SUMMARY OF VENTILATOR STRATEGIES

	CV	HFOV
Initial V_T (ml/kg)*	6–10	–
Initial RR (breaths/min or Hz)	Adjust for pH > 7.15 (max 35)	5 Hz
Initial PEEP (cm H_2O)†	⩾ 10	–
Initial mPaw (cm H_2O)	–	CV + 5
Initial ΔP	–	Adequate chest wall vibration
Initial percentage inspiratory time	33%	33%
Ventilation	↑ RR (max 35) ↑ V_T (max 10 ml/kg)	↑ ΔP ↓ Hz (min 3) Cuff leak
Oxygenation	↑ PEEP (18 cm H_2O) ↑ $F_{I_{O_2}}$ ↑ % I time (max 66%)	↑ mPaw (max 45 cm H_2O) ↑ $F_{I_{O_2}}$
Weaning	↓ $F_{I_{O_2}}$ ⩽ 0.50 ↓ I:E ratio ↓ PEEP Convert to PS wean Breathing trials	↓ $F_{I_{O_2}}$ ⩽ 0.50 ↓ mPaw ⩽ 24 cm H_2O Switch to CV

Definition of abbreviations: CV = conventional ventilation; $F_{I_{O_2}}$ = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; I:E = inspiratory:expiratory; mPaw = mean airway pressure; ΔP = proximal airway pressure amplitude of oscillation; PEEP = positive end-expiratory pressure; PS = pressure support ventilation; RR = respiratory rate in breaths/min or in Hz; V_T = tidal volume.

* The tidal volume is based on actual body weight.

† A minimum PEEP of 18 cm H_2O was required before increasing the inspiratory time.

We designed a randomized, controlled trial comparing HFOV with a CV strategy in adult patients with early-phase ARDS. The specific aim of this trial was to demonstrate the safety and effectiveness of high-frequency oscillatory ventilation and to determine whether it was comparable to CV for the treatment of ARDS in an adult population.

METHODS

Patients

Patients were recruited from October 1997 through December 2000 in 13 university-affiliated medical centers (APPENDIX). The institutional review board at each hospital approved the protocol. Surrogate informed consent was obtained for all patients.

Patients 16 years of age or more who were mechanically ventilated were eligible if they met the following criteria for ARDS: Pa_{O_2}/fraction of inspired oxygen ($F_{I_{O_2}}$) ratio ⩽ 200 mm Hg while on positive end-expiratory pressure (PEEP) ⩾ 10 cm H_2O, bilateral radiographic pulmonary infiltrates, and no clinical evidence of left atrial hypertension (or if available, pulmonary artery occlusion pressure of 18 mm Hg or less). Patients were excluded if they weighed less than 35 kg, had severe chronic obstructive pulmonary disease or asthma, intractable shock, severe airleak (i.e., more than one chest tube per hemithorax with a persistent airleak of more than 120 hours), a nonpulmonary terminal diagnosis with an estimated 6-month mortality of more than 50%, and an $F_{I_{O_2}}$ of more than 0.80 for more than 48 hours, or had participated in other investigational trials for ARDS or septic shock within 30 days.

Ventilator Strategies

Ventilator strategies used are summarized in Table 1. The physiologic targets for the two ventilator treatment arms were similar. The oxygenation goal was an O_2 saturation of 88% or more on $F_{I_{O_2}}$ ⩽ 0.60 with maintenance of mPaw in the HFOV group or PEEP in the CV group until $F_{I_{O_2}}$ could be reduced to 0.60 or less. The target Pa_{CO_2} was between 40–70 mm Hg, although a higher Pa_{CO_2} was tolerated, providing that the pH was more than 7.15. Bicarbonate therapy could be employed for severe respiratory acidosis (pH less than 7.15). Attending physicians oversaw ventilator management and were consulted about major decisions on a 24-hour basis.

TABLE 2. BASELINE PATIENT CHARACTERISTICS

	HFOV	CV
n	75	73
Age, years	48 ± 17	51 ± 18
Actual body weight, kg	78 ± 25	81 ± 26
Ideal body weight, kg*	59.5 ± 10	60.9 ± 10
Sex, % male	52%	64%
APACHE II	22 ± 6	22 ± 9
Sepsis syndrome†	47%	47%
Pulmonary infection	19%	16%
Trauma	21%	18%
Other diagnosis	13%	19%
Air leak	16%	19%
CV prestudy days	2.7 ± 2.7	4.4 ± 7.8
Prestudy CV more than 5 days	22%	36%

Definition of abbreviations: APACHE II = acute physiology, age, and chronic health evaluation score (32); CV = conventional ventilation; HFOV = high-frequency oscillatory ventilation.

Data presented as mean ± SD. None of the differences between groups was statistically significant.

* Ideal body weight for males calculated as 50 + 0.91 (centimeters of height, −152.4) and for females as 45.5 + 0.91 (centimeters of height, −152.4) (31).

† The diagnosis of sepsis syndrome required positive blood culture, latex agglutination test, or other equivalent tests.

TABLE 3. BASELINE PHYSIOLOGIC PARAMETERS

	HFOV	CV
n	75	73
PIP, cm H_2O	39 ± 7	38 ± 8
Mean Paw, cm H_2O	22 ± 5	23 ± 6
PEEP, cm H_2O	13 ± 3	14 ± 3
Respiratory rate, per min	18 ± 5	20 ± 6
Tidal volume, ml/kg	8.2 ± 3	7.8 ± 3
Tidal volume, ml/kg IBW	10.5 ± 2.7	10.1 ± 2.8
$F_{I_{O_2}}$	0.71 ± 0.19	0.72 ± 0.19
Pa_{O_2}, mm Hg	81 ± 6	80 ± 9
Pa_{CO_2}, mm Hg	44 ± 12	45 ± 12
pH	7.37 ± 0.09	7.34 ± 0.11
$Pa_{O_2}/F_{I_{O_2}}$, mm Hg	114 ± 37	111 ± 42
Oxygenation index*	24 ± 15	27 ±19

Definition of abbreviations: CV = conventional ventilation; $F_{I_{O_2}}$ = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; IBW = ideal body weight; Paw = airway pressure; PEEP = positive end expiratory pressure (tidal volume normalized to actual body weight); PIP = peak inspiratory pressure.

*Oxygenation index = (mean Paw × $F_{I_{O_2}}$ × 100/Pa_{O_2}).

None of the differences between the groups were statistically significant. Data are presented as mean ± SD.

TABLE 4. VENTILATOR SETTINGS

	24 Hours		48 Hours		72 Hours	
	HFOV	CV	HFOV	CV	HFOV	CV
n	60	57	55	54	45	48
$F_{I_{O_2}}$	0.51 ± 0.15	0.60 ± 19	0.52 ± 0.17	0.54 ± 0.18	0.51 ± 0.15	0.51 ± 0.17
PIP, cm H_2O	–	37 ± 8	–	38 ± 9	–	37 ± 9
PEEP, cm H_2O	–	13 ± 3	–	13 ± 4	–	13 ± 4
V_T, ml/kg	–	8 ± 2	–	8 ± 3	–	8 ± 2
Mean Paw, cm H_2O	29 ± 6	23 ± 7	28 ± 6	23 ± 8	28 ± 6	22 ± 8
RR, Hz or breaths/min	4.7 ± 0.7	20 ±7	4.7 ± 0.7	19 ± 6	4.5 ± 0.9	19 ± 7
ΔP, cm H_2O	66 ± 14	–	65 ± 13	–	66 ± 17	–

Definition of abbreviations: CV = conventional ventilation; $F_{I_{O_2}}$ = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; ΔP = proximal oscillatory airway pressure amplitude; Paw = airway pressure; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; RR = respiratory rate reported as Hz for HFOV and breaths per minute for CV; V_T = tidal volume normalized to actual body weight.

Data presented as mean ± SD. At 24 hours, data are incomplete for 15 HFOV patients (2 died, 2 exited, 5 moved to CV, and 6 had data unavailable) and 16 CV patients (5 died, 5 exited, and 6 data unavailable). Only the mean Paw was statistically significantly different between groups over the 3 days of treatment ($p < 0.0001$).

HFOV Strategy

The 3100B high-frequency oscillatory ventilator was used (SensorMedics, Yorba Linda, CA). Detailed methods on the use of the 3100B have previously been published (28, 29). HFOV was initiated at the following settings: $F_{I_{O_2}}$ = 0.80–1.00, oscillation frequency = 5 Hz, percent inspiratory time = 33%, and bias flow = 40 L/minute. mPaw was set 5 cm H_2O greater than mPaw during CV immediately before conversion to HFOV. Pressure amplitude of oscillation (ΔP) was initially set to achieve chest wall vibration to the level of the midthigh. ΔP and Hz were sequentially adjusted to achieve Pa_{CO_2} within the target range and maintain a pH of more than 7.15. If maximum ΔP and lowest Hz were insufficient to achieve a pH in the target range, an endotracheal tube cuff leak was allowed to promote additional Pa_{CO_2} elimination. If an $F_{I_{O_2}}$ of more than 0.60 was required to maintain arterial oxygen saturation (Sa_{O_2}) of 88% or more, the mPaw was increased in increments of 2 to 3 cm H_2O every 20 to 30 minutes to a maximum of 40 to 45 cm H_2O. During HFOV, all patients were treated with sedation and neuromuscular blocking agents.

Patients were switched from HFOV back to CV when $F_{I_{O_2}}$ was 0.50 or less, and mPaw was weaned to 24 cm H_2O or less with an Sa_{O_2} of 88% or greater. For transition back to CV, the conventional ventilator was set in the pressure-control mode with peak inspiratory pressure adjusted

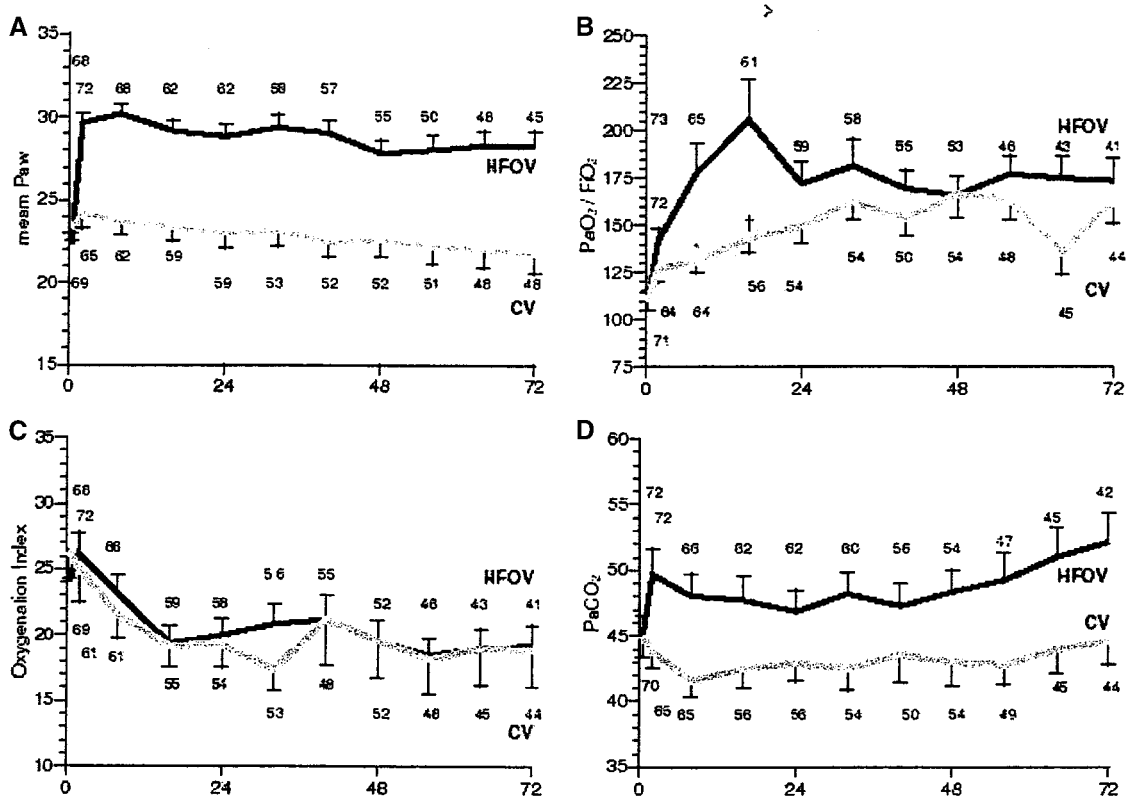

Figure 1. (*A–D*) Differences in four parameters for patients on HFOV (*solid line*) and CV (*slashed line*) over the first 3 study days. *Error bars* represent SEM at each measurement time. *Numbers* above data points denote remaining evaluable patients on assigned ventilator. The differences between mPaw (*A*) and Pa_{CO_2} (*D*) for the two groups over the 3 days were significant ($p < 0.001$ and $p < 0.01$, respectively). $Pa_{O_2}/F_{I_{O_2}}$ (*B*) was significantly higher in the HFOV group at 8 hours (*) ($p = 0.008$) and 16 hours (†) ($p = 0.007$). OI (*C*) decreased in both HFOV and CV groups, which were not significantly different. There were 45 of 73 patients (62%) remaining in the HFOV group and 48 of 73 patients (68%) in the CV group at 72 hours (no significant difference).

TABLE 5. HEMODYNAMIC PARAMETERS IN HFOV AND CV PATIENTS

	Baseline		2 Hours		24 Hours		48 Hours		72 Hours	
	HFOV	CV	HFOV	CV	HFOV	CV	HFOV	CV	HFOV	CV
n	71	73	71	69	67	65	61	57	53	54
Heart rate, beats/min	105 ± 22	107 ± 19	106 ± 22	108 ± 20	97 ± 23	102 ± 20	92 ± 22	96 ± 18	94 ± 22	96 ± 17
Mean BP, mm Hg	80 ± 15	77 ± 13	79 ± 14	77 ± 13	82 ± 14	76 ± 11	77 ± 12	78 ± 18	77 ± 13	77 ± 15
CVP, mm Hg	14 ± 4	16 ± 6	16 ± 9*	15 ± 6	16 ± 5	16 ± 6	17 ± 6	16 ± 5	17 ± 5	15 ± 5
Cardiac output, L/min	7.4 ± 2	7.9 ± 3	7.0 ± 2	7.4 ± 3	6.9 ± 3	7.4 ± 4	6.8 ± 3	7.0 ± 3	7.8 ± 3	7.7 ± 3
PAOP, mm Hg	16 ± 4	17 ± 4	18 ± 3*†	18 ± 5	20 ± 5	18 ± 4	21 ± 7	20 ± 4	19 ± 5	18 ± 5

Definition of abbreviations: CV = conventional ventilation; CVP = central venous pressure; HFOV = high-frequency oscillatory ventilation; mean BP = mean arterial blood pressure; PAOP = pulmonary artery occlusion pressure.

Data are presented as mean ± SD. Numbers represent all surviving patients with hemodynamic and pulmonary artery catheter measurements available at 0 (34 HFOV/30 CV), 2 (31/28), 24 (36/31), 48 (32/24) and 72 hours (23/23). Pulmonary artery catheters were used in 56% and 51% of HFOV and CV patients, respectively (nonsignificant).

* $p < 0.005$ compared with HFOV values at baseline.

† Only PAOP was significantly different between groups over the initial 3 days of treatment ($p = 0.008$).

to achieve a delivered tidal volume of 6 to 10 ml/kg of actual body weight, PEEP of 10 cm H_2O, and inspiratory time of 50%. These settings were designed to achieve a mPaw close to 20 cm H_2O (approximating the mPaw on HFOV just before changing to CV). Subsequent CV weaning was accomplished as outlined in Table 1.

CV Strategy

CV was performed using the pressure-control mode as summarized in Table 1. Final extubation was performed at the discretion of the critical care team and was not protocolized.

Outcome Measures

The primary outcome measure was survival without the need for mechanical ventilation at 30 days after study entry. Secondary outcomes included new or worsening airleak, mucus plugging requiring endotracheal tube change, and 6-month mortality. Patient data, including hemodynamics, ventilator settings, oxygenation data, and evidence of gross barotraumas, were recorded (*1*) at baseline and 2 hours after study entry, (*2*) every 8 hours for the first 3 days on the assigned ventilator, (*3*) subsequently daily while the patient remained on mechanical ventilation.

Statistical Analysis

Sample size was estimated based on data from a previous randomized pediatric HFOV trial (24). A sample size of 148 patients was calculated that would detect a 20% difference in the incidence of key adverse outcomes (e.g., new airleak, intractable hypotension) and provide a 95% confidence interval that the HFOV treatment group was equivalent to or not more than 10% worse than CV. Computerized randomization occurred locally. All analyses were based on intention to treat. Baseline and outcome variables were compared using two-tailed *t* tests for continuous data and difference in proportions for discrete data. Differences in physiologic variables over time between the two treatment groups were evaluated using repeated-measures analysis of variance, which permitted missing data, but data were censored during periods when treatment was not on the assigned ventilator. Differences in the Kaplan-Meier survival curves were evaluated using the Tarone-Ware test. Multivariate analysis of potential predictors of mortality used Cox proportional hazards and logistic regression, the former as the primary test. Baseline parameters in the multivariate analysis included more than 5 days on CV, airleak, sepsis syndrome, diagnosis of pneumonia, other diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II), peak inspiratory pressure, tidal volume/kg, Pa_{CO_2}, pH, Pa_{O_2}/FI_{O_2}, and oxygenation index (OI). Post-treatment response parameters in the multivariate analysis included ventilator group, mPaw, Pa_{O_2}/FI_{O_2}, OI, Pa_{CO_2}, pH, cardiac output, and pulmonary artery occlusion pressure (significance at $p < 0.05$). Analyses were performed using SPSS software (version 10; SPSS, Chicago, IL). Overall results were blinded to the investigators and sponsor throughout the study but were reviewed annually by an independent safety monitoring committee.

RESULTS

Patient Demographics

A total of 148 patients were enrolled and randomized. Patient demographics at study entry are summarized in Table 2. The median length of CV time before enrollment was 1.8 and 2.0 days in the HFOV and CV groups, respectively. Baseline physiologic parameters at study entry for both ventilator strategies are summarized in Table 3. There were no significant differences in any of these parameters between the two groups.

Mechanical Ventilation Settings

Ventilator settings over the first 72 hours after randomization to HFOV and CV are summarized in Table 4. By design, mPaw was significantly higher in the HFOV group at all time points (Figure 1A). Of five patients switched from HFOV to CV within 24 hours, one patient with a head injury was withdrawn to CV for neurologic assessment, two responded to HFOV quickly and were weaned to CV (one of these deteriorated on CV, was returned to HFOV, and later died), one was withdrawn by his attending physician without meeting treatment failure criteria and died 4 days later, and one patient was taken off HFOV at night for unclear reasons but returned to HFOV the next day and was ultimately weaned to CV and survived.

TABLE 6. PRIMARY OUTCOMES: STATUS AT 30 DAYS

	HFOV	CV	p Value	CI*
n	75	73		
Alive with no mechanical ventilation	27 (36%)	23 (31%)	0.686	−12 to 22%
Alive on mechanical ventilation	20 (26%)	12 (16%)	0.190	−4 to 24%
Dead	28 (37%)	38 (52%)	0.102	−32 to 2%

Definition of abbreviations: CI = 95% confidence interval for the difference between groups; CV = conventional ventilation; HFOV = high-frequency oscillatory ventilation.

HFOV does not equal 100% because of rounding.

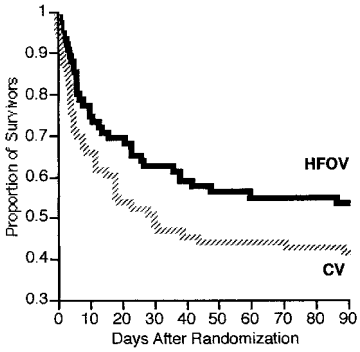

Figure 2. Survival curves showing the proportion of survivors. The *solid line* represents HFOV patients, and the *slashed line* represents CV patients. No enrolled patients died after 89 days. The difference in survival rate did not reach significance at 30 or 90 days ($p = 0.057$ and $p = 0.078$, respectively).

Arterial Blood Gas Response

At 8 and 16 hours, Pa_{O_2}/FI_{O_2} was higher in the HFOV group compared with the CV group (178 versus 131 mm Hg and 205 versus 143 mm Hg, $p < 0.008$ and $p < 0.007$, respectively). Subsequently, the Pa_{O_2}/FI_{O_2} ratio decreased in the HFOV group such that by 24 hours the Pa_{O_2}/FI_{O_2} was not significantly different between treatment groups (Figure 1B). The OI decreased in both groups over the initial 72 hours of the study but was not significantly different between groups (Figure 1C). Pa_{CO_2} was slightly higher in the HFOV patients ($p < 0.001$) throughout the first 72 hours; however, this did not result in significant differences in pH between the two groups (Figure 1D).

Hemodynamic Responses

Pulmonary artery catheters were inserted in 56% (42 of 75) of HFOV patients and 51% (37 of 73) of CV patients. There were no significant differences in heart rate, mean arterial blood pressure, or cardiac output between HFOV and CV groups over the initial 72 hours of treatment (Table 5). Pulmonary artery occlusion pressures were slightly higher in the HFOV group compared with the CV group throughout the initial 72 hours ($p = 0.008$). In the HFOV group, CVP and pulmonary artery occlusion pressures were significantly increased at 2 hours compared with baseline values ($p = 0.003$ and $p = 0.001$, respectively).

Outcomes

The percentage of patients alive and not requiring mechanical ventilation was 36% in the HFOV group and 31% in the CV group ($p = 0.686$) (Table 6). Mortality at Day 30 was 37% in the HFOV group and 52% in the CV group ($p = 0.102$). At 6 months, the mortality rate was 47% in the HFOV group compared with 59% in the CV group ($p = 0.143$) (Figure 2). There were no significant differences in the secondary outcomes evaluated (Table 7). The mean duration of mechanical ventilation was 22 ± 21 and 20 ± 31 days in the HFOV and CV groups, respectively. The mean duration of HFOV was 6 ± 6 days. Causes of death were similar in both patient groups and are summarized in Table 8.

Adjunctive Therapies

The protocol was not designed as a crossover study; however, patients in either group could be treated with the alternate form of ventilation if treatment failure criteria were met and/or the attending physicians felt that additional therapies could potentially be life saving. Of the 75 patients randomized to HFOV, 7 (9%) received rescue therapies. Four received inhaled nitric oxide. Two were proned. One received high-dose corticosteroids (i.e., more than 2 mg/kg methylprednisolone equivalent), and four were treated with CV. The 30-day mortality in these patients was 71% (five of seven).

Of the 73 patients randomized to CV, 12 (16%) received rescue therapies. Eight were treated with inhaled nitric oxide, nine were treated with HFOV, three were proned, and four received high-dose corticosteroids. The 30-day mortality of these patients was 50% (6 of 12). There was no significant difference in mortality between HFOV and CV treatment groups who received adjunctive therapies.

Protocol Compliance

As a measure of compliance, we reviewed all data points during the first 72 hours and at the time of transition from HFOV to CV (for HFOV patients). We found excellent compliance (99% HFOV and 100% CV) with the oxygenation strategy outlined for both treatment groups. Compliance with the strategies outlined for ventilation was 97% in the HFOV group and 99% in the CV group. The arterial pH was more than 7.15 in 97% and 93% of the HFOV and CV groups, respectively.

Predictors of Survival

OI response was the most significant post-treatment predictor of mortality irrespective of assigned ventilator (Figure 3). Stepwise logistic regression of the OI trend identified 16 hours as the most significant time point ($p = 0.001$). Multivariate analysis identified four parameters that significantly predicted 30-day mortality irrespective of assigned ventilator group: more than 5 pretreatment days on CV ($p = 0.032$), APACHE II ($p = 0.002$), baseline pH (0.049), and OI at 16 hours ($p = 0.001$).

TABLE 7. SECONDARY OUTCOMES

	HFOV	CV
Intractable hypotension, %*	0 (0%)	2 (3%)
Oxygenation failure†	4 (5%)	6 (8%)
Ventilation failure‡	4 (5%)	6 (8%)
Air leak developed or worsened§	7 (9%)	9 (12%)
Mucus-plugged ET tube‖	4 (5%)	3 (4%)
Six-month mortality	35 (47%)	43 (59%)
Six-month mechanical ventilation	0 (0)%	2 (3%)

Definition of abbreviations: CV = conventional ventilation; ET = endotracheal tube; HFOV = high-frequency oscillatory ventilation.

* Intractable hypotension is defined as a mean arterial blood pressure of less than 60 mm Hg for 4 hours or 50 mm Hg for 1 hour despite adequate ventricular preload and vasopressor support.

† Oxygenation failure is defined as an oxygenation index of 42 or more after 48 hours of treatment.

‡ Ventilation failure is defined as a pH ≤ 7.15 for 6 hours and a bicarbonate of 19 meq/L or more.

§ Air leak defined as a pneumothorax, pneumomediastinum, pneumopericardium or pneumoperitoneum.

‖ Mucus-plugged endotracheal tube is defined as requiring replacement of endotracheal tube.

None of the differences are statistically significant.

TABLE 8. CAUSES OF 30-DAY MORTALITY

	HFOV	CV
n	25	36
Cardiac arrest	16%	17%
Multiple organ failure	56%	50%
Sepsis	40%	36%
Profound hypoxemia	16%	16%
Other	16%	17%
Care withdrawn	21%	30%

Definition of abbreviations: CV = conventional ventilation; HFOV = high-frequency oscillatory ventilation.

Totals do not equal 100% because of multiple-associated causes of death. Cause of death was not available for five patients. Differences between groups were not statistically significant.

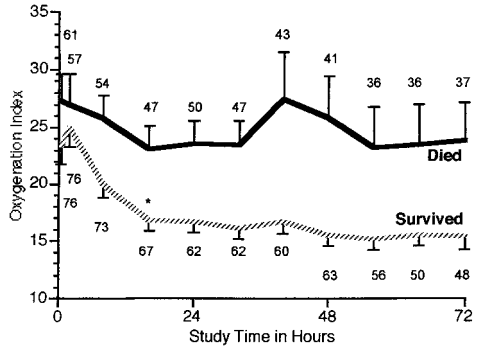

Figure 3. Differences in OI for survivors (*slashed line*) and nonsurvivors (*solid line*) over the first 3 study days. *Error bars* represent SEM at each measurement time. *Numbers* above data points denote remaining patients on assigned ventilator. The difference between OI for the two groups over the 3 days was highly significant ($p < 0.0001$). Survivors showed an improvement over the period, whereas nonsurvivors did not ($p = 0.014$). *The point of best discrimination was at 16 hours ($p < 0.001$). There was no significant difference related to ventilator assignment.

DISCUSSION

The main purpose of this study was to evaluate prospectively the safety and efficacy of HFOV compared with CV in adult patients with ARDS. We found that the use of HFOV applied with an "open-lung" approach is safe and is not associated with adverse hemodynamic effects. The higher mPaw applied during HFOV compared with the CV group likely explains the early (less than 24 hours) improvement in Pa_{O_2}/FI_{O_2} and slightly higher central venous and pulmonary artery occlusion pressures observed in the HFOV group. Alternatively, the slightly higher CVP and pulmonary artery occlusion pressures could also have been related to increased fluid administration after initiation of HFOV, although we did not quantitate fluid balance prospectively. The cause of the apparent decrease in Pa_{O_2}/FI_{O_2} ratio in the HFOV group after the initial improvement noted at 8 and 16 hours is unclear. Similar numbers of patients exited both treatment groups over the first 72 hours of treatment.

Although this study was not powered to evaluate mortality, HFOV was associated with a nonsignificant trend toward reduced mortality at 30 days and 6 months. Although there were no significant differences in baseline characteristics of patients before randomization, there was a nonsignificant trend toward increased pre-enrollment days on CV, decreased pH, and increased OI in the patients randomized to CV, which may have contributed to the observed mortality. Assuming the same trend had continued, we would have needed to enroll a total of 199 patients to achieve a p value of less than 0.05. The study design (i.e., to test equivalency between ventilator strategies) did not provide for continued enrollment beyond the agreed on sample size.

Multivariate analysis found that the OI trend was the most significant post-treatment predictor of survival irrespective of assigned ventilator. This is consistent with some (24, 27, 33) but not all (28) previous studies reporting treatment responses to HFOV. Interestingly, the baseline OI has previously been found to be predictive in adult patients on CV (after controlling for nonpulmonary organ dysfunction) (34). Although the OI response at 16 hours was the most discriminating time point in our study, we would not suggest this be used as a clinical guideline until prospectively validated. Failure of the OI to improve might serve to identify patients in future prospective trials who might be candidates for other adjunctive therapies.

There were no significant differences between treatment groups in adverse events or multiorgan failure. In particular, the incidence of new or worsening airleak was similar to that observed in other studies evaluating ventilator strategies in ARDS (7, 35, 36).

To interpret the results of this study in the context of recent trials evaluating ventilator strategies for ARDS, one needs to evaluate carefully the severity of illness and etiological factors for enrolled patients (37, 38). The recently published ARDS Network trial (n = 861 patients) comparing a volume-cycled "lung protective" low tidal volume strategy (6 ml/kg ideal body weight) with a higher tidal volume strategy (12 ml/kg ideal body weight) reported a 30-day mortality of 31% and 39.8%, respectively, in the two treatment groups (7, 39). Patients entered into the ARDS Network trial had a higher Pa_{O_2}/FI_{O_2}, lower PEEP levels, a lower OI, and a lower prevalence of sepsis than our study. The initial mPaw of 17 cm H_2O in the ARDS Network trial (compared with 23 cm H_2O in our study) would have been below the severity threshold for which we would generally initiate HFOV. These differences may explain the 30-day mortality difference between the treatment groups in our study and the ARDS Network treatment groups.

Although there was an emerging consensus that a lower pressure and tidal volume strategy might be lung protective and achieve a lower mortality in ARDS, when our study was designed (1997), there was disagreement on the exact pressures and tidal volumes that should be used (40, 41). We did not prospectively stratify patients based on inspiratory plateau pressure at the time of randomization. One of the limitations of our CV strategy was the use of a tidal volume algorithm based on actual rather than ideal body weight. Additionally, we did not specify a limit for inspiratory plateau pressure or peak pressure or strictly protocolize extubation. In the future, HFOV should be compared with the current "gold-standard" CV strategy such as the low tidal volume strategy used in the ARDS Network trial (42).

The ability of HFOV to maintain an "open-lung" using lower peak airway pressures and smaller tidal volumes than those applied during CV may potentially result in less "biotrauma" and ventilator-induced lung injury (19, 20). Future comparative trials of HFOV should include markers of lung biotrauma such as interleukin-6 (1).

It appears that of all the current interventions available for clinicians to treat patients with severe ARDS, the ventilator techniques used may ultimately have the largest impact on outcomes (43, 44). This study supports the hypothesis that HFOV is safe and as effective as the CV strategy to which it was compared in this trial. Further studies are warranted to determine the ideal patients and optimal techniques of applying HFOV (45–50).

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APPENDIX

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