Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome

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Objective: **To evaluate the safety and efficacy of high-frequency oscillatory ventilation (HFOV) in adult patients with the acute respiratory distress syndrome (ARDS) and oxygenation failure.**

Design: **Prospective, clinical study.**

Setting: **Intensive care and burn units of two university teaching hospitals.**

Patients: **Twenty-four adults (10 females, 14 males, aged 48.5 ± 15.2 yrs, Acute Physiology and Chronic Health Evaluation II score 21.5 ± 6.9) with ARDS (lung injury score 3.4 ± 0.6, Pao_2/FIo_2 98.8 ± 39.0 mm Hg, and oxygenation index 32.5 ± 19.6) who met one of the following criteria: $Pao_2 \leq 65$ mm Hg with $FIo_2 \geq 0.6$, or plateau pressure ≥35 cm H_2O.**

Interventions: **HFOV was initiated in patients with ARDS after varying periods of conventional ventilation (CV). Mean airway pressure (P_{aw}) was initially set 5 cm H_2O greater than P_{aw} during CV, and was subsequently titrated to maintain oxygen saturation between 88% and 93% and $FIo_2 \leq 0.60$.**

Measurements and Main Results: **FIo_2, P_{aw}, pressure amplitude of oscillation, frequency, blood pressure, heart rate, and arterial blood gases were monitored during the transition from CV to HFOV, and every 8 hrs thereafter for 72 hrs. In 16 patients who had pulmonary artery catheters in place, cardiac hemodynamics were recorded at the same time intervals. Throughout the HFOV trial, P_{aw} was significantly higher than that applied during CV. Within 8 hrs of HFOV application, and for the duration of the trial, FIo_2 and $Paco_2$ were lower, and Pao_2/FIo_2 was higher than baseline values during CV. Significant changes in hemodynamic variables following HFOV initiation included an increase in pulmonary artery occlusion pressure (at 8 and 40 hrs) and central venous pressure (at 16 and 40 hrs), and a reduction in cardiac output throughout the course of the study. There were no significant changes in systemic or pulmonary pressure associated with initiation and maintenance of HFOV. Complications occurring during HFOV included pneumothorax in two patients and desiccation of secretions in one patient. Survival at 30 days was 33%, with survivors having been mechanically ventilated for fewer days before institution of HFOV compared with nonsurvivors (1.6 ± 1.2 vs. 7.8 ± 5.8 days; $p = .001$).**

Conclusions: **These findings suggest that HFOV has beneficial effects on oxygenation and ventilation, and may be a safe and effective rescue therapy for patients with severe oxygenation failure. In addition, early institution of HFOV may be advantageous. (Crit Care Med 2001; 29:1360–1369)**

KEY WORDS: acute respiratory distress syndrome; mechanical ventilation; high-frequency ventilation; high-frequency oscillation; respiratory failure

Conventional ventilatory strategies may induce further lung damage in patients with lung injury. The lungs of animals ventilated with large tidal volumes and high peak airway pressures show severe alterations in permeability, pulmonary edema, and diffuse alveolar damage very similar to the pathologic findings observed in patients with the acute respiratory distress syndrome (ARDS) (1, 2). Inadequate end-expiratory alveolar recruitment may also contribute to lung injury, as other animal studies have clearly shown that shear forces generated during repetitive opening and closing of lung units at end expiration result in lung injury (1–3); and the addition of positive end-expiratory pressure significantly reduces alveolar hemorrhage, edema formation, and protein leak (1–5). Further, injurious ventilatory strategies are associated with higher levels of pulmonary and systemic inflammatory mediators (5–7), which may predispose patients to multiple system organ failure (8).

Several clinical studies have supported the findings from animal studies. The National Institutes of Health National Heart, Lung, and Blood Institute ARDS network recently completed a multicenter randomized trial of 6 mL/kg vs. 12 mL/kg tidal volume ventilation in patients with acute lung injury/ARDS, and found that the low-volume group had significantly more ventilator- and organ failure-free days, and a 22% reduction in mortality compared with the high-volume group (9). Amato et al. (10, 11) also demonstrated benefits in gas exchange, lung recovery, and weaning rate using a lung-protective ventilation strategy consisting of positive end-expiratory pressure greater than the lower inflection point, tidal volume <6 mL/kg (with permissive hypercapnia), volume recruitment maneuvers, and peak inspiratory pressures <40 cm H_2O, when prospec-

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tively compared with a conventional ventilation strategy (tidal volume 12 mL/kg). In addition, they observed a significant reduction in 30-day mortality in patients treated using this lung-protective strategy.

Thus, current ventilatory objectives in patients with ARDS include both optimizing gas exchange and preventing further lung injury. Accomplishing the latter goal is ideally done by preventing both end-expiratory alveolar collapse and end-inspiratory overdistension, however, during conventional ventilation (CV) such an approach may result in hypercapnia with potential adverse consequences (12). In theory, high-frequency oscillatory ventilation (HFOV)—applied using an open lung approach—may accomplish these objectives better than conventional mechanical ventilation and provide effective CO_2 elimination. During HFOV, a mean airway pressure (P_{aw}), usually higher than that used during CV, is applied to achieve and maintain lung recruitment, even at end expiration. In addition, HFOV delivers very small tidal volumes at extreme rates, thus avoiding the large alveolar pressure and volume excursions typical of CV. Moreover, by optimizing alveolar recruitment and thus ventilation perfusion matching, the use of HFOV may allow reductions in delivered oxygen to less toxic levels.

Animal studies show that HFOV applied using an open lung approach, compared with CV, improves gas exchange, preserves surfactant, and reduces lung injury, lavage granulocytes, and inflammatory mediators (13–16). However, minimization of lung injury with HFOV requires maintenance of an adequate alveolar volume with an appropriate mean P_{aw} that prevents derecruitment and atelectasis (16, 17). In humans, the majority of clinical trials evaluating HFOV have been conducted in the neonatal population (18–27). Although none of the pediatric randomized, controlled trials have demonstrated any survival benefit with HFOV, infants treated with HFOV demonstrated improvements in oxygenation, were exposed to less oxygen (21, 24), and had less chronic lung disease at 30 days when compared with those treated conventionally (23, 24). Published experience with HFOV in adults is limited to a single prospective observational study in which Fort et al. (28) evaluated the safety and efficacy of HFOV in 17 adults with ARDS failing inverse ratio ventilation. This group demonstrated significant improvements in gas exchange and reductions in F_{IO_2} requirements in the majority of patients.

The specific aim of this study was to prospectively evaluate the safety and efficacy of HFOV in adults with severe ARDS and oxygenation failure.

MATERIALS AND METHODS

The study was performed in the intensive care unit (ICU) of Mt. Sinai Hospital and in the intensive care and burn units of St. Michael's Hospital, Wellesley site, both in Toronto, Ontario, Canada. Given that HFOV was considered a rescue therapy for patients failing conventional ventilation, the need for informed consent was waived.

Patient Selection. Patients with ARDS who met the following entry criteria were considered eligible for inclusion in the study: age >16 yrs, body weight >35 kg, and intubated and failing CV, as defined by one of the following criteria: $Pa_{O_2} \leq 65$ mm Hg with $F_{IO_2} \geq 0.6$, or plateau pressure ≥ 35 cm H_2O. ARDS was considered to be present if the patient had diffuse bilateral infiltrates on the chest radiograph, a ratio of Pa_{O_2} to F_{IO_2} of <200 mm Hg, and no clinical evidence of left ventricular failure. Patients were excluded from enrollment if they had historical and/or clinical evidence of left ventricular failure or severe obstructive lung disease.

Ventilator. The ventilator used was an adult high-frequency oscillatory ventilator (3100B, Sensormedics, Yorba Linda, CA). The 3100B uses an oscillating diaphragm, creating both an active inspiratory and expiratory phase, and does not require a specialized endotracheal tube for ventilation. The 3100B differs from the 3100A, the model used in neonates and children, in that it has a higher maximal bias flow (up to 50 L/min), a higher maximum pressure amplitude of oscillation (ΔP), a more powerful electromagnet allowing for a faster acceleration to ΔP, a larger diameter patient circuit tubing, and a cooling system. The ΔP is determined by the set "power," as well as the compliance and resistance of the patient's respiratory system. The 3100B uses a servo-controlled, heated wick humidifier (MR730 Humidifier, Fisher Paykel Healthcare, Auckland, New Zealand) in line with the bias flow. Confirmation of adequate humidification was achieved by noting condensation on the diaphragm and along the inspiratory tubing.

Study Protocol. This was a prospective uncontrolled trial. All patients were ventilated with either volume- or pressure-controlled ventilation before institution of HFOV. All patients received continuous infusions of morphine and a benzodiazepine (lorazepam or midazolam) during HFOV. In addition, the majority of patients received neuromuscular blocking agents, starting before and continuing throughout HFOV. When neuromuscular blocking agents were used, dosing was titrated to achieve one to two twitches out of a train of four stimuli to the ulnar nerve. All patients had arterial catheters in place, and a pulmonary artery catheter was inserted by the medical team caring for the patient if clinically indicated.

In all patients, HFOV was initiated at the following settings: an F_{IO_2} of 0.8–1.0, an oscillation frequency of 5 Hz, a percent inspiratory time of 33%, and a bias flow of 40 L/min. Mean P_{aw} was set 5 cm H_2O greater than the P_{aw} during CV immediately before conversion to HFOV, and ΔP was titrated to vibrate the chest wall from the clavicles to the mid-thigh region. ΔP was subsequently titrated to maintain Pa_{CO_2} in the target range.

The target Pa_{CO_2} was 35–60 mm Hg, although a higher Pa_{CO_2} was tolerated if the pH was >7.15. If the Pa_{CO_2} was >60 mm Hg and pH <7.15, the power setting was increased to a maximum of 10 to increase ΔP; ΔP is also a function of respiratory system compliance and resistance. If adequate ventilation could not be achieved at the maximum pressure amplitude, the following interventions were used in sequence: 1) reduction of respiratory frequency in 0.5- to 1-Hz steps to a minimum of 3 Hz, and 2) deflation of the endotracheal tube cuff. If, as a consequence of endotracheal tube cuff deflation, delivered P_{aw} was reduced, bias flow was increased as needed to maintain P_{aw}.

Target oxygenation parameters were pulse oximetry (Sp_{O_2}) of 88% to 93%, and $F_{IO_2} \leq 0.60$. Once the patient was stabilized on HFOV, F_{IO_2} was reduced until Sp_{O_2} was between 88% and 93%. If at any time the F_{IO_2} required to maintain Spo2 between 88% and 93% was >0.60, the P_{aw} was increased in increments of 1–2 cm H_2O until $F_{IO_2} \leq 0.60$ maintained the Sp_{O_2} in the desired range, or the chest radiograph showed evidence of hyperinflation, defined as flattened diaphragms bilaterally and more than ten ribs visible posteriorly. If the Sp_{O_2} was below the target range, P_{aw} was increased first up to a maximum of 40 cm H_2O, or until the chest radiograph showed hyperinflation, and then F_{IO_2} was increased as needed to maintain Sp_{O_2} in the desired range.

General Medical Management. General medical management, including the use of fluids, antibiotics, steroids, and vasopressor agents, was directed by the ICU team caring for the patient. All patients remained semirecumbent (30°) during the duration of the study; and no patients were ventilated in the prone position. Tracheal suctioning was achieved by placing an in-line suction catheter (Trach Care, 14-Fr, Ballard Medical Products, Draper UT) between the endotracheal tube and the ventilator circuit. Suctioning could be performed at any time by nursing or respiratory therapy personnel. Inhaled nitric oxide (INO) could be introduced if F_{IO_2} remained ≥ 0.70 during HFOV, despite maximal P_{aw}. INO was weaned and withdrawn once F_{IO_2} was ≤ 0.50.

Weaning/Withdrawal from HFOV. Patients were considered as HFOV failures if they had ventilation failure ($Paco_2$ >60 mmHg and pH ≤7.15, despite maximal ΔP and other interventions), oxygenation failure (Spo_2 <88% despite maximal mean P_{aw} and Fio_2), or suffered intractable hypotension unresponsive to adequate preload or inotropic support.

As the patients' oxygenation improved, the Fio_2 was reduced to maintain Spo_2 between 88% and 93%. Once Fio_2 was ≤0.60, P_{aw} was decreased in 1- to 2-cm H_2O decrements, alternating with reductions in Fio_2 of 0.05–0.10, as long as Spo_2 remained within the target range. Patients were switched from HFOV back to CV when Fio_2 ≤0.40, P_{aw} was ≤25 cm H_2O, and suctioning and manual bagging resulted in minimal oxyhemoglobin desaturation (<5%), and rapid recovery in oxygenation (<60 secs).

If, after withdrawal of HFOV, the patient deteriorated and once again met inclusion criteria, HFOV could be reinstituted. If reinstitution of HFOV occurred within 48 hrs, the data were included with the initial HFOV trial data. If the duration of time between HFOV trials was >48 hrs, the second trial was included in the data as a separate trial.

Physiologic Outcome Variables. The primary outcome measure was physiologic improvement. Blood pressure, heart rate, ventilator settings, and arterial blood gases were recorded during CV just before initiating HFOV, and then every 8 hrs during HFOV for a total duration of 72 hrs. Oxygenation index ($OI = [Fio_2 \cdot P_{aw} \cdot 100]/Pao_2$), and Pao_2/Fio_2 ratios were calculated at the same time intervals. If a pulmonary artery catheter was in place, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), and thermodilution cardiac output (CO) were recorded at the same time intervals. Mean P_{aw}, inspiratory time, ΔP, and frequency were recorded from the visual display on the 3100B ventilator. Fio_2 was measured using an in-line analyzer (MiniOX III, Catalyst Research, Owings Mills, MD). Acute Physiology and Chronic Health Evaluation (APACHE) II (29) and lung injury scores (LIS) (30) were determined at the start of HFOV.

Other Outcome Variables. Secondary outcome measures included HFOV oxygenation and/or ventilation failure, duration of HFOV, and ICU mortality. Patients were monitored for complications such as hypotension, desiccation of secretions assessed during suctioning and/or fiberoptic bronchoscopy, and mucous plugging, as well as evidence of air leaks, including subcutaneous emphysema, pneumothorax, pneumomediastinum, and pneumopericardium. Hypotension was defined by one of the following: systolic blood pressure (SBP) <90 mm Hg, or a reduction in SBP >20% immediately after institution of HFOV, or a reduction in SBP >20% following an increase in P_{aw} during HFOV compared with the SBP immediately before the change.

Statistical Methods. Mixed model repeated measures analyses (31) were used to determine whether Pao_2/Fio_2 ratio, $Paco_2$, OI, Fio_2, and P_{aw} were significantly different at initiation of HFOV, and 8–48 hrs after HFOV compared with CV. A first-order autoregressive covariance structure was specified to model the covariance within subjects. This structure implies that adjacent observations on the same subject have a higher correlation than observations that are farther apart. Residuals, specifically the observed values minus predicted values, were used to assess the fitted models. All missing data were considered to be missing at random. Univariate logistic regression was used to determine whether baseline characteristics were predictive of ICU survival. Because of low power considerations, multiple logistic regression was not performed (32). All analyses were performed using SAS System version 7.0 for Windows (SAS Institute, Cary, NC). Data are expressed as mean ± SD. A $p < .05$ was considered significant.

RESULTS

From September 1997 to November 1999, 24 patients with ARDS and severe hypoxemia underwent 27 trials of HFOV (Table 1). The etiology of ARDS included pneumonia and/or sepsis (n = 13), severe burns (n = 5), bone marrow transplant (n = 4), aspiration of gastric contents (n = 1), and amniotic fluid embolus (n = 1). In the burn patients, the mean total body surface area affected by second- and/or third-degree burns was 47.5%. At baseline, the mean age and APACHE II score were 48.5 ± 15.2 yrs (range, 21–78 yrs) and 21.5 ± 6.9, respectively. All patients had severe ARDS, as noted by a mean LIS of 3.4 ± 0.6, a mean Pao_2/Fio_2 of 98.8 ± 39.0 mm Hg, and an OI of 32.5 ± 19.6. During CV before HFOV initiation, average values for positive end-expiratory pressure, plateau pressure, and mean P_{aw} were 14.5 ± 2.4, 36.8 ± 4.2, and 24.3 ± 3.1 cm H_2O, respectively.

Mean P_{aw} and Gas Exchange. Mean P_{aw} during HFOV was significantly higher throughout the study than mean P_{aw} at baseline during CV (Fig. 1*A*). As part of the study protocol, Fio_2 was increased immediately after HFOV initiation (Fig. 1*B*), and this first value was significantly higher than Fio_2 during CV. However, within 8 hrs of HFOV, there was a significant reduction in Fio_2 compared with that during CV, and this significant difference persisted for the remaining study duration (Fig. 1*B*). Within 8 hrs of HFOV application, and for the majority of the trial, $Paco_2$ was lower (Fig. 2) than the mean value measured during CV. Figure 3 demonstrates changes in mean Pao_2/Fio_2 ratio and OI over the 72-hr study duration. Compared with the baseline value during CV, the mean Pao_2/Fio_2 improved significantly by 8 hrs and remained elevated throughout the study period (Fig. 3*A*). At 8 hrs, the group's mean percentage improvement in the

Table 1. Patients' characteristics at study entry

No. of patients	24
No. of HFOV trials	27
Age, yrs	48.5 ± 15.2
Sex, male/female	14/10
APACHE II	21.5 ± 6.9
LIS	3.4 ± 0.6
Ventilation prior to HFOV, days	5.7 ± 5.6
$Paco_2$, mm Hg	55.7 ± 32.3
Fio_2	0.78 ± 0.21
Pao_2/Fio_2, mm Hg	98.8 ± 39.0
Oxygenation index[a]	32.5 ± 19.6
Airway pressures during conventional ventilation	
Plateau, cm H_2O	36.8 ± 4.2
PEEP, cm H_2O	14.5 ± 2.4
Mean, cm H_2O	24.3 ± 3.1
Diagnosis	
Pneumonia/sepsis	13
Burn	5
Bone marrow transplant	4
Gastric aspiration	1
Amniotic fluid embolus	1

HFOV, high-frequency oscillatory ventilation; APACHE II, Acute Physiology and Chronic Health Evaluation II; LIS, lung injury score (30); PEEP, positive end-expiratory pressure.

[a]Oxygenation index = $Fio_2 \cdot P_{aw} \cdot 100/Pao_2$, where P_{aw} is mean airway pressure. Values represent means ± SD.

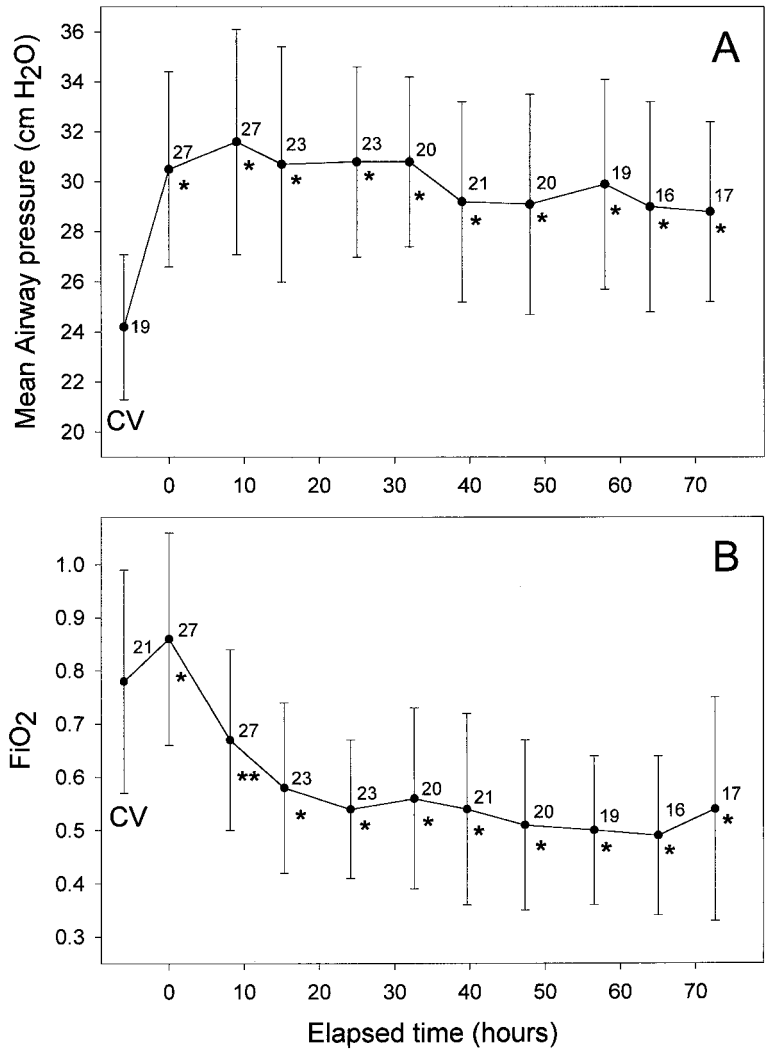

Figure 1. Mean airway pressure (*A*) and F_{IO_2} (*B*) plotted over the study duration. *CV* represents values observed during conventional ventilation immediately before initiating high-frequency oscillatory ventilation (HFOV); all subsequent measurements are during HFOV. Time 0 represents values observed within 30 mins of HFOV initiation. Values represent means ± SD. Numbers adjacent to each data point represent number of trials. *$p \leq .0003$ and **$p = .03$ compared with measured values during CV.

Pa_{O_2}/F_{IO_2} ratio compared with baseline was 26.4%. Although OI showed a downward trend throughout the study, mean values were not significantly lower than the baseline value until 48 hrs, but remained lower than the baseline value for the remainder of the study (Fig. 3*B*).

Hemodynamic Variables. Table 2 lists hemodynamic variables immediately before and during the first 48 hrs of HFOV. Sixteen patients had a pulmonary artery catheter in place during the HFOV trial. At baseline, patients who had a pulmonary artery catheter were not different from those without a pulmonary artery catheter with regard to age, APACHE II, LIS, F_{IO_2}, Pa_{O_2}/F_{IO_2}, OI, ventilator pressures, or number of ventilator days before HFOV. Pa_{CO_2} was significantly higher at baseline in the patients without a pulmonary artery catheter (78 vs. 47; $p = .048$).

Because many patients did not have a pulmonary artery catheter in place or had it removed before study termination, data for mean pulmonary artery pressure, PAOP, and CO are limited. As a group, initiation and maintenance of HFOV did not induce any significant change in mean systemic blood pressure. The mean heart rate also remained stable until 32 hrs after initiation of HFOV and then showed significant reductions compared with baseline. In those patients with a pulmonary artery catheter in place, mean values for mean pulmonary artery pressure did not change significantly during HFOV. Central venous pressure increased immediately after starting HFOV, however, the difference was statistically significant only at 16 and 40 hrs. PAOP was significantly higher than the recorded value during CV at 8 and 40 hrs after the initiation of HFOV. Cardiac output decreased significantly immediately after starting HFOV, and remained lower than the baseline value throughout the study, however, the comparison with baseline was not statistically significant at all time points. Despite the reduction, the CO remained within a normal range throughout the study, and no changes in blood pressure, heart rate, or vasopressor requirements were noted.

Weaning/Withdrawal of HFOV. Table 3 details patient outcomes on HFOV. Only one patient, a 25-yr-old neutropenic woman who had undergone bone marrow transplantation, met the criteria for oxygenation failure during HFOV. Despite a maximal P_{aw} of 37 cm H_2O and F_{IO_2} of 1.0, her Pa_{O_2} remained in the 50s and low 60s. INO was initiated at 97 hrs; however, the patient died secondary to profound hypoxemia. One patient with ARDS resulting from blastomycosis pneumonia was withdrawn from HFOV at 114 hrs for ventilation failure, and he died on the following day of multiple organ failure. In addition to these two patients, HFOV was discontinued in ten others because the decision was made to withdraw life support because of poor prognosis, despite satisfactory oxygenation and ventilation. No patient required discontinuation of HFOV for hypotension.

Ten patients (42%) improved and were successfully weaned from HFOV. Two patients were withdrawn from HFOV because of technical problems. During HFOV use in a burn patient, the driver diaphragm failed because of overheating of the 3100B ventilator. However, this incident occurred before the modification of the cooling system in the 3100B, and the high ambient temperature in the burn unit (>37°C) likely contributed to the problem. In another patient, the low battery indicator malfunctioned and alarmed continuously, necessitating discontinuation of HFOV.

Complications and Other Outcomes. One patient had intermittent oxyhemoglobin desaturations secondary to mucous plugs that were documented on fiberoptic bronchoscopy and during tracheal suctioning. Two patients developed pneumothoraces during HFOV, and both were treated with thoracostomy

tube insertion. One of these patients had an acute oxyhemoglobin desaturation on day 17 of his second HFOV trial, and P_{aw} was increased from 30 to 33 cm H_2O, and F_{IO_2} was increased from 0.65 to 1.0. After these changes, a chest radiograph revealed a large left pneumothorax. The second patient, a woman with ARDS secondary to amniotic fluid embolus, developed a large right pneumothorax immediately after endotracheal tube insertion and being placed on HFOV. However, the initial chest radiograph revealed that the tip of the endotracheal tube was in the right mainstem bronchus.

Equipment failure occurred in three patients. Two of these patients are described in "Weaning/Withdrawal of HFOV." In the third patient, the plastic "bellows" housing cracked, causing an abrupt reduction in the delivered P_{aw}, but the housing was easily replaced and did not require discontinuation of HFOV.

Neuromuscular blocking agents were administered continuously during HFOV to all patients except two. One patient who was receiving minimal sedation was alert and interactive during HFOV, and denied any respiratory discomfort. However, during spontaneous breathing, her inspiratory effort caused a reduction in circuit P_{aw} below the preset lower limit of 5 cm H_2O, and the 3100B terminated oscillation, as it interpreted the low P_{aw} as a circuit disconnection. By design, the 3100B has insufficient flow to meet adult patients' inspiratory demands. Another patient receiving large doses of intravenous sedation did not make any spontaneous respiratory efforts when the neuromuscular blockade was discontinued.

No patients were placed in the prone position, and no patients received corticosteroid treatment for ARDS during HFOV. Four patients received INO at a dose of 5–10 parts per million during the first 72 hrs of HFOV. In three patients, INO was initiated at 10, 1, and 4 hrs after starting HFOV, and was discontinued at 17, 16, and 12 hrs, respectively. In the fourth patient, INO was started at 16 hrs and continued for the duration of HFOV. Four additional patients had INO initiated >72 hrs after starting HFOV.

Eight (33%) patients survived to be discharged from the ICU and from the hospital. If the nine patients either with burns or who had undergone bone marrow transplants, all of whom died, are excluded, survival in the remaining patients (n = 15) was 53%. In the majority of patients, the cause of death was withdrawal of life support because of hopeless prognosis, or multiple organ failure.

Survivors vs. Nonsurvivors. Table 4 shows the baseline characteristics of survivors and nonsurvivors before initiating HFOV. Survival at 30 days was 33%. All five patients with burns died during their ICU stay. Four survivors and four nonsurvivors were treated with INO at some time during HFOV. Age, APACHE II, LIS, and ventilator parameters during CV were similar between the two groups. In addition, similar percentages of survivors and nonsurvivors had pulmonary artery catheters placed (Table 4). At baseline, we found that the mean number of ventilator days before HFOV was significantly higher in the nonsurvivor group, at 7.8 ± 5.8 days, compared with 1.6 ± 1.2 days in the survivors ($p = .001$). In addition, nonsurvivors had lower mean Pa_{O_2}/F_{IO_2}, and higher F_{IO_2}, Pa_{CO_2}, and OI than survivors, however, these differences did not reach statistical significance. Figure 4 illustrates the temporal course of changes in Pa_{CO_2} after initiation of HFOV in both survivors and nonsurvivors. Although the nonsurvivors demonstrated significant reductions in Pa_{CO_2} during HFOV compared with baseline, their mean Pa_{CO_2} was higher than Pa_{CO_2} in the survivors throughout the study duration. Figure 5 shows the temporal changes in OI and Pa_{O_2}/F_{IO_2} in survivors and nonsurvivors. Although OI was observed to decrease in both groups, only the nonsurvivor group demonstrated significant reductions at every time point compared with baseline. However, by 16 hrs, and for the remainder of the study, mean OI was lower in survivors than nonsurvivors. Pa_{O_2}/F_{IO_2} increased significantly in both groups over the study duration, but was consistently higher in survivors than nonsurvivors beyond 20 hrs (Fig. 5*B*).

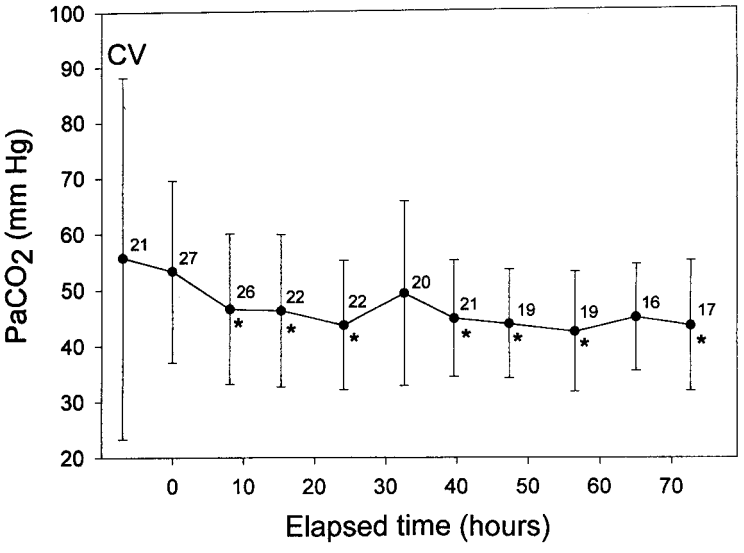

Figure 2. Pa_{CO_2} plotted over the study duration. *CV* represents Pa_{CO_2} observed during conventional ventilation immediately before initiating high-frequency oscillatory ventilation (HFOV); all subsequent measurements are during HFOV. Time 0 represents Pa_{CO_2} observed within 30 mins of HFOV initiation. Values represent means ± SD. Numbers adjacent to each data point represent number of trials. *$p <$ .05 compared with Pa_{CO_2} measured during CV.

DISCUSSION

The main purpose of the present study was to assess the efficacy and safety of HFOV, applied using a lung recruitment strategy, in adult patients with severe ARDS and oxygenation failure. Three main observations were made. First, HFOV was associated with improved oxygenation and ventilation, as well as reduced F_{IO_2} requirements. Second, the incidence of barotrauma in ARDS patients treated with HFOV was similar to the reported incidence in patients treated conventionally (9, 33, 34). Finally, compared with nonsurvivors, patients surviving to hospital discharge had been ventilated conventionally for significantly fewer days before being treated with HFOV.

Our observations in 24 patients are very similar to those reported by other investigators (28, 35). In 17 patients with severe ARDS (LIS 3.81 ± 0.23, Pa_{O_2}/F_{IO_2} 68.6 ± 21.6 mm Hg), Fort and colleagues

(28) used an HFOV strategy in which P_{aw} was incrementally increased to achieve an oxygen saturation ≥90% and F_{IO_2} ≤0.60. They observed significant improvements in gas exchange in 13 patients, although objective criteria for improvement were not defined. In addition, patients demonstrated significant reductions in OI and F_{IO_2} requirements for the 48-hr duration of the study, and suffered no significant hemodynamic impairment. Survival at 30 days was 47%, with survivors having lower baseline LIS and OI, and higher baseline Pa_{O_2}/F_{IO_2} than nonsurvivors. As in the present study, compared with nonsurvivors, survivors in the Fort study had been conventionally ventilated for significantly fewer days before HFOV.

Although published experience with HFOV in adults is limited, ten randomized controlled trials in neonatal/pediatric patients with respiratory distress syndrome or ARDS have yielded conflicting results. Five of these trials failed to show any oxygenation benefit of HFOV compared with CV (18, 19, 22, 25, 26), three because they failed to emphasize lung volume recruitment and, in contrast to the current study, did not use higher mean P_{aw} during HFOV compared with

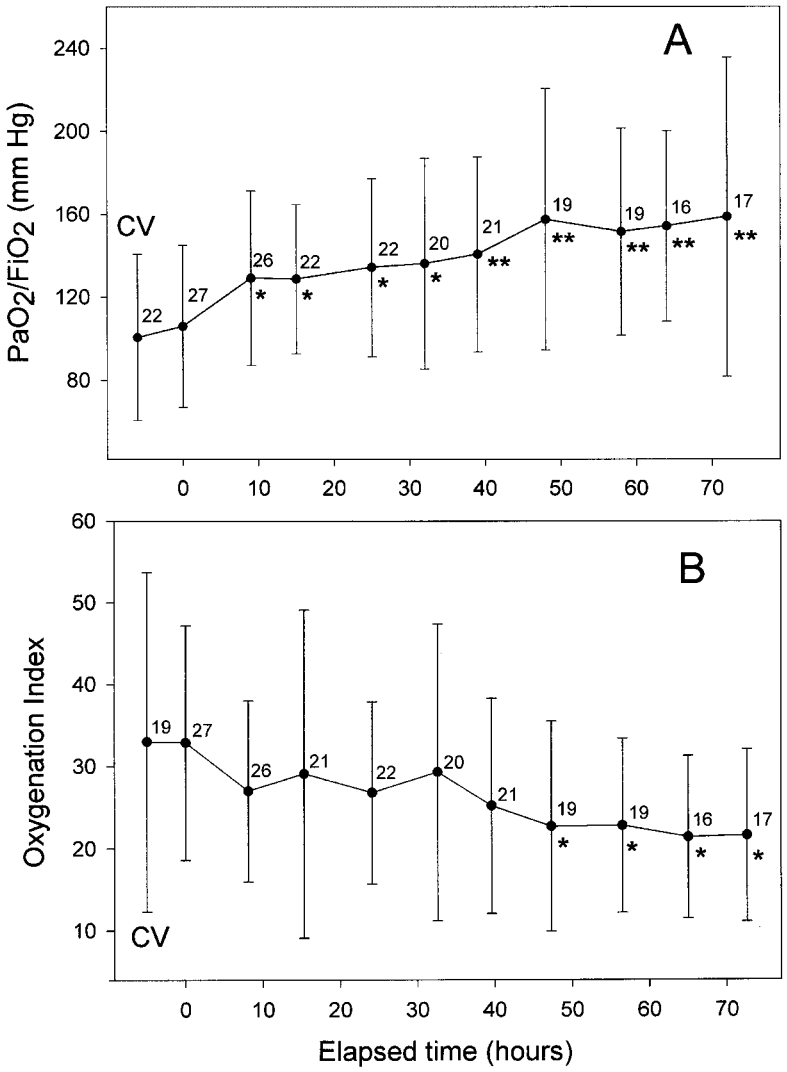

Figure 3. Pa_{O_2}/F_{IO_2} ratio (*A*) and oxygenation index (*B*) plotted over the study duration. *CV* represents values observed during conventional ventilation immediately before initiating high-frequency oscillatory ventilation (HFOV); all subsequent measurements are during HFOV. Time 0 represents values observed within 30 mins of HFOV initiation. Values represent means ± SD. Numbers adjacent to each data point represent number of trials. $*p < .05$ and $**p < .005$ compared with calculated values during CV.

Table 3. Patient outcomes on high-frequency oscillatory ventilation (HFOV)

Duration of HFOV, days	1 to >10
HFOV failures	
Oxygenation	1
Ventilation	1
Complications	
Pneumothorax	2
Equipment failure	3
Desiccation of secretions	1
Reason for withdrawal of HFOV	
Successfully weaned	10
Withdrawal of life support/death	12
Technical problem	2
ICU survival, no. (%)	8 (33)
Nonburn patients, no./total (%)	8/19 (42)
Burn patients, no./total	0/5
Hospital survival, no. (%)	8 (33)
Cause of death	
Withdrawal of life support	8
Multiple organ failure	6
Hypoxemia	1
Cardiac arrhythmia	1

ICU, intensive care unit.

Table 2. Changes in hemodynamic variables during high-frequency oscillatory ventilation (HFOV)

	CV	0 Hrs[a]	8 Hrs	16 Hrs	24 Hrs	32 Hrs	40 Hrs	48 Hrs
Heart rate, beats/min	106 ± 15 (24)	105 ± 16 (27)	102 ± 17 (27)	107 ± 21 (23)	103 ± 27 (23)	100 ± 20 (20)[b]	98 ± 22 (21)[b]	95 ± 14 (20)[c]
MAP, mm Hg	81 ± 21 (24)	80 ± 19 (27)	85 ± 20 (27)	86 ± 17 (23)	84 ± 16 (23)	82 ± 14 (20)	86 ± 20 (21)	85 ± 18 (20)
MPAP, mm Hg	31 ± 7 (15)	30 ± 6 (10)	31 ± 6 (10)	35 ± 7 (6)	34 ± 13 (4)	33 ± 10 (4)	37 ± 7 (5)	38 ± 7 (5)
PAOP, mm Hg	16 ± 4 (15)	16 ± 5 (15)	22 ± 7 (12)[b]	19 ± 5 (9)	17 ± 7 (6)	17 ± 3 (7)	22 ± 10 (6)[b]	18 ± 6 (7)
CO, L/min	10.1 ± 3.6 (13)	7.7 ± 2.5 (12)[b]	6.2 ± 2.2 (4)	8.5 ± 3.2 (11)[b]	7.3 ± 2.1 (6)[b]	6.6 ± 2.6 (7)[c]	6.2 ± 2.1 (5)[b]	7.2 ± 1.8 (6)
CVP, mm Hg	13.8 ± 5.1 (16)	14.9 ± 5.4 (17)	17.5 ± 5.9 (15)	15.6 ± 4.7 (11)[b]	15.3 ± 4.9 (8)	15.9 ± 3.5 (9)	18.2 ± 6.5 (9)[b]	17.3 ± 4.7 (11)

CV, variables recorded during conventional mechanical ventilation immediately prior to HFOV; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output.

[a]0 Hrs represents values immediately after initiating HFOV; [b]$p < .05$ and [c]$p < .005$ compared with CV value. Values represent means ± SD. Numbers of patients are in parentheses.

Table 4. Baseline characteristics of survivors and nonsurvivors prior to high-frequency oscillatory ventilation (HFOV)

	Survivors	Nonsurvivors
No. of patients	8 (8 NB)	16 (11 NB, 5 B)
Age, yrs	49.1 ± 19.0	48.1 ± 13.7
Sex, male/female	3/5	11/5
APACHE II	23.1 ± 6.7	20.7 ± 7.0
LIS	3.4 ± 0.5	3.4 ± 0.7
Ventilation prior to HFOV, days	1.6 ± 1.2	7.8 ± 5.8[a]
$Paco_2$, mm Hg	43.0 ± 20.5	61.2 ± 35.5
Pao_2/Fio_2, mm Hg	110.2 ± 22.9	93.2 ± 44.5
Oxygenation index[b]	22.5 ± 10.4	37.5 ± 21.4
Pulmonary artery catheter, no. (%)	7 (88)	11 (69)
Ventilator parameters during CV		
Plateau pressure, cm H_2O	35.0 ± 5.3	37.6 ± 3.5
PEEP, cm H_2O	15.1 ± 1.6	14.2 ± 2.7
Mean airway pressure, cm H_2O	23.0 ± 3.5	25.0 ± 2.8
Fio_2	0.67 ± 0.16	0.83 ± 0.22

NB, non-burn patients; B, burn patients; LIS, lung injury score (30); CV, conventional ventilation; PEEP, positive end-expiratory pressure.

[a] $p = .001$; [b] oxygenation index = $Fio_2 \cdot P_{aw} \cdot 100/Pao_2$, where P_{aw} is mean airway pressure. Values represent means ± SD.

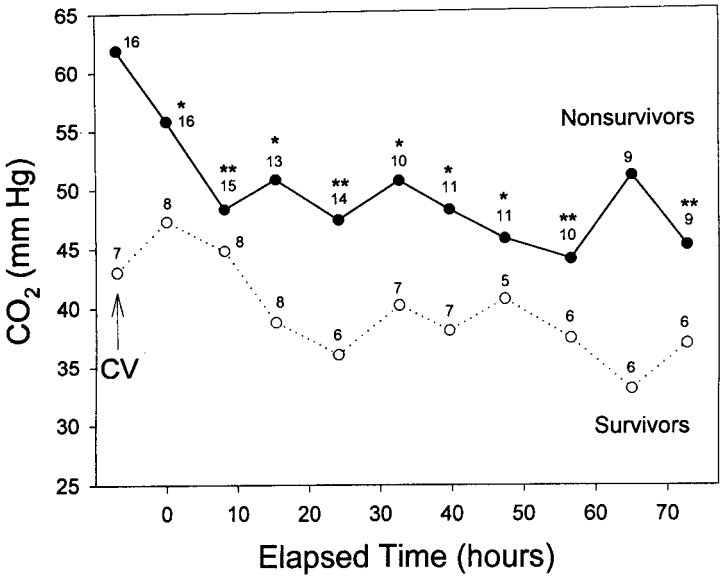

Figure 4. Time course of changes in $Paco_2$ after initiation of high-frequency oscillatory ventilation (HFOV) in both survivors (*open circles*) and nonsurvivors (*closed circles*). *CV* represents values observed during conventional ventilation immediately before initiating HFOV; all subsequent measurements are during HFOV. Time 0 represents $Paco_2$ observed within 30 mins of HFOV initiation. Numbers adjacent to each data point represent number of trials. *$p < .05$ and **$p < .005$ compared with $Paco_2$ during CV.

CV (18, 22, 25). In a study by Clark et al. (19), although no differences in gas exchange were detected between the HFOV and CV groups, the data were skewed in part by the effectiveness of HFOV in those neonates crossed over from CV, who were included in the CV group during analysis. Thome et al. (26) conducted a large, well-designed multicenter study that applied both recruitment maneuvers and consistently higher P_{aw} in the HFOV group than in the CV group throughout the 240-hr observation period. Nevertheless, there were no observed differences in gas exchange, chronic lung disease, or mortality in the two groups, and the HFOV group had more air leaks (42% vs. 31%; $p = .04$) than the CV group. A possible explanation for the lack of demonstrated benefit of HFOV in their study was the use of a less injurious CV strategy than in other studies, with lower peak airway pressures and tidal volumes, higher respiratory frequencies, and permissive hypercapnia. In addition, these investigators enrolled smaller infants, who are most at risk for death and chronic lung disease, than previous trials (21, 22, 24, 25). Finally, approximately 50% of infants in both arms met treatment failure criteria, in which case the choice of ventilatory management was left to the attending physician.

Other recent clinical studies of HFOV in neonatal and pediatric patients have offered more encouraging results. All four trials that have demonstrated an oxygenation benefit with HFOV have emphasized lung volume recruitment, as we did in the current study, with the application of higher P_{aw} during HFOV than during CV (20, 21, 23, 24). Although none of the trials have demonstrated any survival benefit with HFOV, they are all underpowered to do so. However, patients treated with HFOV were exposed to lower Fio_2 (21, 24), required a shorter duration of oxygen therapy (23, 24), and had less chronic lung disease at 30 days when compared with the groups treated conventionally (22–24, 27). Although one trial found that infants treated with HFOV were significantly more likely to have a poor neurologic outcome (18), the other controlled studies reported either no difference (22, 23), or a significant reduction in pulmonary and nonpulmonary complication rates using HFOV (21, 24).

Survivors vs. Nonsurvivors. Because this was an uncontrolled study evaluating HFOV as rescue therapy in patients with severe oxygenation failure, it was not designed to evaluate survival. Nonetheless, overall survival in the current study was 33%. Of the patients who died, the majority died as a result of withdrawal of life support because of a grim prognosis, or multiple organ failure. The mortality rate in the current study is higher than that in the study by Fort and colleagues (28), despite higher APACHE II scores in their cohort. However, mortality in our study is similar to mortality reported in trials evaluating outcome in patients with ARDS (36, 37). In addition, given that HFOV was used as rescue therapy in ARDS patients who had failed CV, a high mortality rate is not unexpected. Moreover, a large number of patients in the current study were recipients of bone marrow transplants or had severe burns, factors that are associated with an increased mortality but are not captured by the APACHE II scoring system (29). Excluding the patients with burns and those

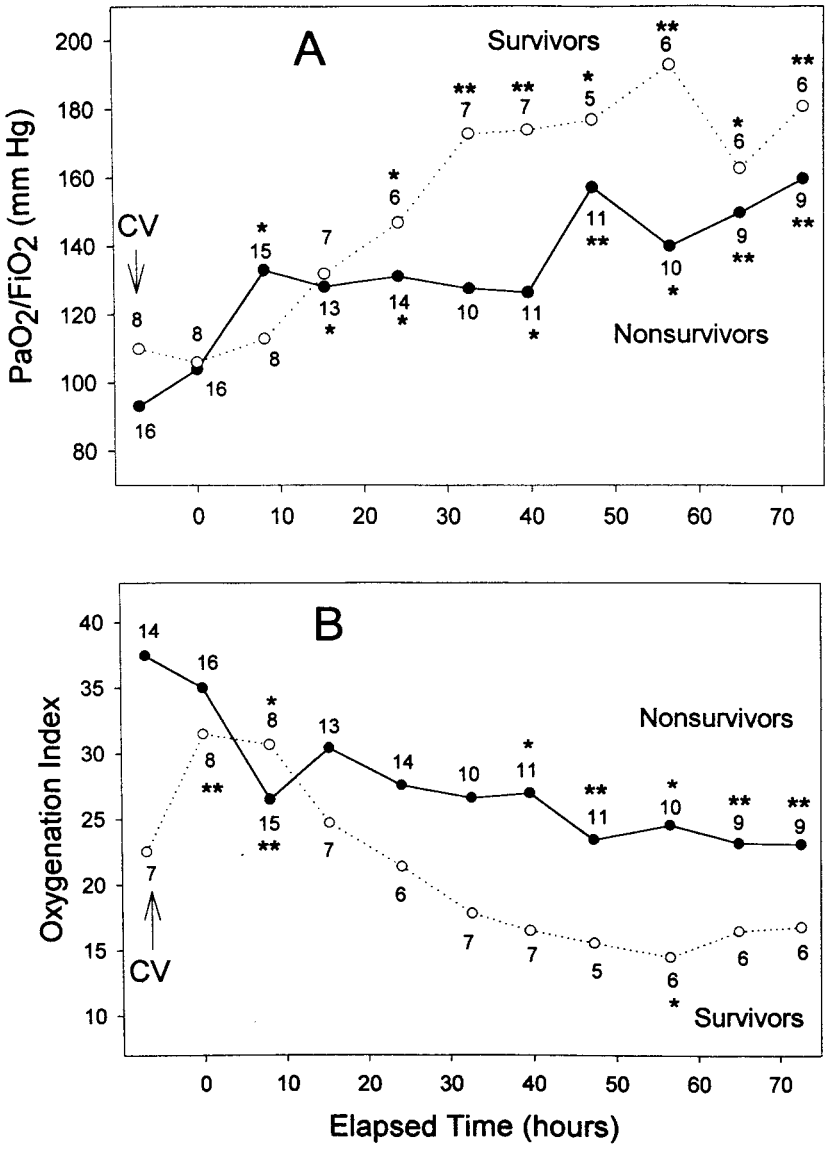

Figure 5. Time course of changes in oxygenation index (OI) and Pao_2/Fio_2 after initiation of high-frequency oscillatory ventilation (HFOV) in both survivors (*open circles*) and nonsurvivors (*closed circles*). *CV* represents values observed during conventional ventilation immediately before initiating HFOV; all subsequent measurements are during HFOV. Time 0 represents OI and Pao_2/Fio_2 observed within 30 mins of HFOV initiation. Numbers adjacent to each data point represent number of trials. $*p < .05$ and $**p < .005$ compared with OI and Pao_2/Fio_2 during CV.

who had undergone bone marrow transplant, survival in the current study was 53%.

We found that the number of days of conventional ventilation before HFOV was a significant prognostic factor for mortality and that nonsurvivors had been ventilated conventionally for a greater number of days before HFOV than survivors. Other investigators have made very similar observations (28, 35). Multiple well-designed animal studies show that exposure to high peak airway pressures, large tidal volumes, or end-expiratory pressures insufficient to prevent alveolar collapse causes further lung injury (1–3). Thus, patients with a longer duration of exposure to CV before HFOV may have worse lung injury and more parenchymal fibrosis with fewer recruitable lung units. In support of this hypothesis are at least two animal studies that have demonstrated difficulty in achieving alveolar expansion after exposure to CV (38, 39).

The question arises as to whether the longer duration of mechanical ventilation before HFOV is an indication of greater severity of illness at baseline in the nonsurvivor group. In support of this possibility are the more severe gas exchange abnormalities ($Paco_2$, OI, and Pao_2/Fio_2 ratio) in nonsurvivors at baseline and throughout the study. However, these differences were not statistically significant, and other baseline measures of illness severity (APACHE II, LIS) were not different at baseline between the two groups. Moreover, given that we had specific criteria for inclusion in the study, we think it is unlikely that the nonsurvivor group was more ill at baseline, and consider the potential benefit of early intervention with HFOV very provocative.

We found that response to HFOV at 8 or 24 hrs, defined as a 20% improvement in OI or Pao_2/Fio_2 ratio, was not predictive of survival. In addition, we were unable to identify any baseline patient characteristics that predicted sustained oxygenation improvement in response to HFOV.

Hemodynamics. With the application of higher P_{aw} during HFOV than during CV, we observed a reduction in CO along with increases in PAOP and central venous pressure. Despite the reduction, the CO remained within a normal range throughout the study, and no changes in blood pressure, heart rate, or vasopressor requirements were noted. In addition, although we did not measure lactate levels, patients did not develop worsening acidosis during the study duration. The increase in PAOP and central venous pressure is likely related to changes in transmural pressures during HFOV, however, without direct measurements of intrathoracic pressure, we cannot confirm this.

Few prior studies have evaluated the impact of HFOV on hemodynamics, and the findings are contradictory. Although Fort et al. (28) observed an increase in PAOP during HFOV, they observed no change in CO or other hemodynamic indices during the transition from CV to HFOV, similar to the results of some pediatric studies (40, 41). In contrast, two pediatric studies found significant reductions in CO measured noninvasively in infants converted from CV to HFOV (42, 43), in the absence of changes in systemic blood pressure (43).

The American-European Consensus definition of acute lung injury/ARDS includes a PAOP ≤18 mm Hg (44), however, recent trials have demonstrated that a PAOP >18 mm Hg is common in patients who meet the radiographic and oxygenation criteria for ARDS (45, 46). Our data also support this finding, and demonstrate that measured PAOP can in-

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crease above the defined ARDS range with manipulations of intrathoracic pressure.

Complications. In the current study, the use of HFOV was not associated with complications in excess of those observed during CV. The incidence of pneumothorax in the current study was 8.3%, which is similar to rates observed by other investigators in observational studies (34) as well as in studies evaluating new ventilatory strategies in ARDS (9, 33, 47).

Future Considerations. In this study, we applied HFOV using a lung recruitment strategy with mean P_{aw} higher than those applied during CV. It is clear from animal studies that for optimal outcome using HFOV, once atelectatic alveoli are recruited, an appropriate P_{aw}, above the closing pressure of airways and alveoli, is essential to maintain alveolar recruitment (15). However, it appears that a sustained inflation to total lung capacity is required to initially achieve alveolar recruitment (14, 48). Despite the evidence from these animal studies, recruitment maneuvers have not been routinely applied during HFOV. Recruitment maneuvers have been shown in a recent uncontrolled trial to be safe and effective in adults during CV (49), and, if used routinely during HFOV trials, may improve the observed oxygenation response.

Defining optimal lung inflation remains problematic, making it difficult to compare results of different studies. We, like other investigators, have used clinical end points including oxygenation, shunt fraction, hemodynamics, and the chest radiograph to titrate mean P_{aw}. Possible future methods of evaluating optimal lung inflation include computed tomography and measurements of lung/respiratory system compliance as well as functional residual capacity.

In conclusion, HFOV has beneficial effects on oxygenation and ventilation and may be a safe and effective rescue therapy for patients with severe oxygenation failure when instituted early. HFOV seems to conform with current recommendations for a lung-protective strategy, in that P_{aw} greater than those pressures usually tolerated on CV can be used to maintain alveolar recruitment without hemodynamic compromise and without exposing the lung to high peak pressures. The encouraging recent results strongly support the need for a prospective, randomized trial of "ideal" conventional ventilation vs. HFOV in adults with ARDS. Perhaps such a comparison will require very early randomization, before the occurrence of extensive lung injury, and should be performed in large centers experienced in the use of HFOV.

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