

High-Frequency Oscillatory Ventilation in Adults*

The Toronto Experience

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Study objectives: To review the clinical experience with high-frequency oscillatory ventilation (HFOV) in three medical-surgical ICUs in Toronto, ON, Canada, and to describe patient characteristics, HFOV strategies, and outcomes.

Design and patients: Retrospective chart review of all patients treated with HFOV at three academic university-affiliated ICUs since 1998. The data extracted included patient demographics, etiology of respiratory failure, ventilator settings, and gas exchange and cardiovascular data from baseline to 72 h of treatment, as well as at the transition from HFOV to conventional ventilation (CV). Heart rate and BP were recorded at regular intervals in all patients, and hemodynamic data were recorded in 32 patients who had pulmonary artery catheters in place. Cointerventions and ICU mortality were also recorded.

Measurements and results: A total of 156 adults (67 women and 89 men; mean [\pm SD] age, 48 ± 18 years; mean acute physiology and chronic health evaluation [APACHE] II score, 23.8 ± 7.5) with severe ARDS (*ie*, mean P_{aO_2} /fraction of inspired oxygen [F_{IO_2}] ratio, 91 ± 48 mm Hg; mean oxygenation index [OI], 31 ± 14) who had received CV for a duration of 5.6 ± 7.6 days underwent 171 trials of HFOV. HFOV was discontinued within 4 h in 19 patients (12%) because of difficulties with oxygenation, ventilation, or hemodynamics. P_{aO_2}/F_{IO_2} ratios and OI ($[F_{IO_2} \times \text{mean airway pressure} \times 100]/P_{aO_2}$) improved significantly with the application of HFOV, and this benefit persisted for the 72-h study duration. Significant changes in hemodynamics following HFOV initiation included an increase in central venous pressure and a reduction in cardiac output (throughout the 72 h), and an increase in pulmonary artery occlusion pressure (at 3 and 6 h). Patients were treated with HFOV for 5.1 ± 6.3 days. The 30-day mortality rate was 61.7%. Pneumothorax occurred in 21.8% of patients, 43.6% of patients were treated with inhaled nitric oxide, and 37.2% of patients were treated with steroids. Independent predictors of mortality on multivariate analysis were older age, higher APACHE II score, lower pH at the initiation of HFOV, and a greater number of days receiving CV prior to HFOV.

Conclusions: HFOV has beneficial effects on P_{aO_2}/F_{IO_2} ratios and OI, and may be an effective rescue therapy for adults with severe oxygenation failure. The early institution of HFOV may be advantageous. (*CHEST* 2004; 126:518–527)

Key words: ARDS; high-frequency oscillation; high-frequency ventilation; mechanical ventilation; respiratory failure

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; CO = cardiac output; CV = conventional ventilation; CVP = central venous pressure; F_{IO_2} = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; INO = inhaled nitric oxide; LIS = lung injury score; MODS = multiple organ dysfunction score; mPaw = mean airway pressure; NO = nitric oxide; OI = oxygenation index; PAOP = pulmonary artery occlusion pressure

High frequency oscillatory ventilation (HFOV) is an alternative method of ventilation that theoretically achieves the goals of lung protective ventilation. During HFOV, gas exchange occurs through the application of a constant mean airway pressure (mPaw) that is usually higher than that applied during conventional ventilation (CV).¹ Theoretically, HFOV may lead to improved alveolar recruitment

while avoiding both the cyclic closing and opening of alveolar units and the high peak airway pressures that occur with CV. The potential adverse effects of HFOV include cardiovascular compromise or barotrauma from the higher airway pressures.

The theoretical benefits of HFOV over CV are supported by the results of animal studies. In primates and surfactant-deficient rabbits, the use of

HFOV leads to improved gas exchange, more uniform lung inflation, and reduced histopathologic evidence of ventilator-induced lung injury.²⁻⁴ The potential importance of reduced alveolar cycling and lung distention is supported by other animal studies, in which the use of HFOV was associated with reduced levels of inflammatory mediators when compared to CV, despite the use of similar mPaw levels.⁵⁻⁷ In the neonatal and pediatric population, HFOV, utilizing an aggressive volume recruitment strategy, results in improvements in oxygenation compared with CV.^{8,9} Despite the use of higher mPaw levels in these trials, HFOV appears to be associated with a lower incidence of ventilator-associated lung injury, as indicated by a lower incidence of barotrauma and a decreased requirement for supplemental oxygen at 30 days.⁸⁻¹¹ Importantly, this physiologic benefit may lead to improved patient outcomes, as demonstrated by a trial¹¹ showing a reduction in ventilator days and mortality with the use of HFOV in very low-birth-weight infants.

In adults with ARDS, the experience with HFOV is limited to five observational studies¹²⁻¹⁶ and one randomized controlled trial.¹⁷ The observational studies¹²⁻¹⁶ reported significant improvements in oxygenation using an aggressive open lung strategy during HFOV, and the two larger studies^{12,13} suggested better outcomes when HFOV is applied early in the course of ARDS. Derdak and colleagues¹⁷ conducted a multicenter randomized, controlled trial comparing HFOV with conventional pressure control ventilation strategy in 148 adults with early-phase ARDS. Applying a significantly higher mPaw in the HFOV group, there was an early improvement in the PaO₂/fraction of inspired oxygen (FIO₂) ratio compared with the conventional group. However, this difference did not persist beyond 24 h. The mortality rate in the HFO group was 37%, compared with 52% in the CV group, but this difference was not statistically significant. They concluded that

HFOV is a safe and effective mode of ventilation for the treatment of ARDS in adults.

HFOV is increasingly employed in ICUs for patients with ARDS who remain hypoxemic during conventional therapy. Our goal was to review the experience with HFOV in three academic university-affiliated medical surgical ICUs in Toronto, Canada, and to describe patient characteristics, HFO ventilator strategies, the safety of the technique, patient outcomes, and potential predictors of outcome.

MATERIALS AND METHODS

Three University of Toronto-affiliated medical centers with extensive experience using HFOV in adults participated in this retrospective descriptive study of their practice patterns and outcomes. The three centers were Mount Sinai Hospital, University Health Network, and Sunnybrook & Women's College Health Sciences Center. All of the ICUs use an adult high-frequency oscillatory ventilator (model 3100B; SensorMedics; Yorba Linda, CA). In general, HFOV is used in these centers as rescue therapy for patients who remain hypoxemic and require high levels of inspired oxygen during CV. There was no standard protocol in place for the initiation, titration, or weaning of HFOV. The recorded data included patient demographics, etiology of respiratory failure, comorbidities, ventilator settings, and blood gas and cardiovascular data from baseline to 72 h of treatment. The study was approved by the institutional review board of each hospital. Data from 33 of these patients have been included in previous reports.^{13,17,18} We have included them in the current study to report on the largest clinical experience possible, and to capitalize on the higher statistical power of the larger population to identify small but potentially important clinical effects.

HFOV was introduced into each center between 1998 and 1999. Data were extracted from the records of all patients who were treated at each center, from the time of introduction until January 2002. The data were reviewed by individuals not involved with data extraction, were entered into a database, and were screened for aberrant entries. Statistical analysis was performed in two prospectively defined steps. First, summary data were tabulated with means, SDs, and percentages, as appropriate, and the trends of ventilator settings and physiologic variables were evaluated with repeated-measures analysis of variance. A *t* test was used to evaluate the changes from baseline compared with specific time points. In the second step, differences in baseline risk and HFOV response associated with survival were explored. Logistic regression was used to identify significant baseline characteristics associated with mortality. A repeated-measures analysis of covariance was used to identify which HFOV response variables were associated with mortality. For those response variables found to be significantly associated with mortality, stepwise logistic regression was used to determine at which specific time that variable was most significantly associated with mortality. Finally, these significant response variables were stepped into the baseline logistic regression equation to determine whether the response was significant, while controlling for baseline status. One exploratory *post hoc* analysis also was conducted to identify a dichotomous indication of mortality associated with oxygenation index (OI). We used the *t* test and χ^2 test, as appropriate. The analysis of variance used a maximum likelihood method, so that patients would not be excluded if data were not available for all time periods. Statistical analysis was performed using two statistical software packages (SPSS, versions 10 and 11; SPSS; Chicago, IL; and GB-STAT, version 4.5;

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RESULTS

From January 1998 to February 2002, 156 patients with ARDS and severe hypoxemia underwent 171 trials of HFOV (Table 1). The mean (\pm SD) duration of ARDS prior to HFOV was 3.5 ± 4.3 days (median duration, 2 days; 25 to 75% confidence interval [CI], 0.2 to 5 days). The etiology of ARDS included sepsis (88 patients), pneumonia (26 patients), and aspiration of gastric contents (8 patients). All patients had severe ARDS, as evidenced by a mean lung injury score (LIS) of 3.5 ± 0.4 , a mean $\text{PaO}_2/\text{FIO}_2$ ratio of 91 ± 48 mm Hg, and an OI of 31.2 ± 13.7 . Airway pressures during CV immediately prior to HFOV are presented in Table 1.

MPaw and Gas Exchange

The applied mPaw was significantly higher during HFOV than was mPaw at baseline during CV (Fig 1,

Table 1—Patient Characteristics*

Characteristics	Values
Patients, No.	156
HFOV trials, No.	171
Age, yr	47.8 ± 18.3
Sex	
Male	89
Female	67
Weight, kg	71.2 ± 19.4
APACHE II	
1st 24 h in ICU	23.8 ± 7.5
24 h prior to HFOV	23.9 ± 7.9
MODS	9.4 ± 3.6
LIS	3.5 ± 0.4
ARDS prior to HFOV, d	3.5 ± 4.3
Ventilation prior to HFOV, d	5.6 ± 7.6
Gas exchange during conventional ventilation	
PaCO_2 , mm Hg	53.0 ± 18.9
FiO_2	0.86 ± 0.17
$\text{PaO}_2/\text{FIO}_2$ ratio, mm Hg	91.2 ± 47.6
OI†	31.2 ± 13.7
Airway pressures during conventional ventilation, cm H_2O	
Plateau	36.0 ± 6.5
PEEP	14.0 ± 3.2
mPaw	24.0 ± 5.1
ARDS etiology	
Sepsis	88 (60)
Pulmonary infection	26 (17.7)
Aspiration	8 (5)
Pancreatitis	3 (2)
Trauma	3 (2)
Other	19 (12.1)

*Values given as No. (%) or mean \pm SD. PEEP = positive end-expiratory pressure.

†OI = $\text{FiO}_2 \times \text{mPaw} \times 100/\text{PaO}_2$.

top left, A). As part of a general HFOV strategy, FIO_2 was increased immediately after HFOV initiation (Fig 1, *top right, B*), and consequently this first value was significantly higher than the FIO_2 during CV. Within 3 h of receiving HFOV, and for up to 72 h, there was a significant reduction in FIO_2 compared with CV (Fig 1, *top right, B*). Compared with the baseline value during CV, the mean $\text{PaO}_2/\text{FIO}_2$ ratio continued to improve for the first 12 h and remained stable beyond that time (Fig 1, *bottom left, C*). At 12 h, the mean improvement of the group in $\text{PaO}_2/\text{FIO}_2$ ratio compared with baseline was 63 mm Hg (*ie*, a 70% improvement). OI was significantly lower than baseline at 12 h, and remained lower for the remainder of the study (Fig 1, *bottom right, D*). PaCO_2 was well-controlled during HFOV, and by 48 h it was significantly lower than the baseline value (PaCO_2 during CV, 53 mm Hg; PaCO_2 at 48 h, 50 mm Hg; $p = 0.026$).

Hemodynamic Variables

Figure 2 illustrates the hemodynamic variables immediately prior to and during the first 72 h of therapy with HFOV. As a group, heart rate decreased, systolic pressure increased, and diastolic pressure was unchanged throughout the study period.

Thirty-two patients (20.5%) had a pulmonary artery catheter during HFOV. At baseline, patients with a pulmonary artery catheter did not differ from those without a PA catheter with regard to age, acute physiology and chronic health evaluation (APACHE) II score, LIS, FIO_2 , $\text{PaO}_2/\text{FIO}_2$ ratio, OI, PaCO_2 , ventilator pressures, or ventilator days prior to HFOV. Central venous pressure (CVP) increased immediately after starting therapy with HFOV and remained higher than the value during CV throughout the 72 h ($p = 0.01$) [Fig 2, *bottom, B*]. Pulmonary artery occlusion pressure (PAOP) was significantly greater than the baseline value at 3 h after initiation of HFOV ($p = 0.03$) and 6 h after initiation of HFOV ($p = 0.03$), but the difference did not persist beyond 6 h. Cardiac output (CO) decreased significantly immediately after starting therapy with HFOV and remained lower than the baseline value throughout the study ($p = 0.0043$), but it was within the normal range.

HFOV Weaning and Transition to CV

Seventy-seven patients (48.7%) improved with HFOV and were successfully weaned to CV after 6.1 ± 5.5 days. Only 33% of these patients died, but they averaged 23.3 ± 21.2 days of therapy with HFOV and CV. From HFOV initiation until transition to CV, there were small changes in the mean

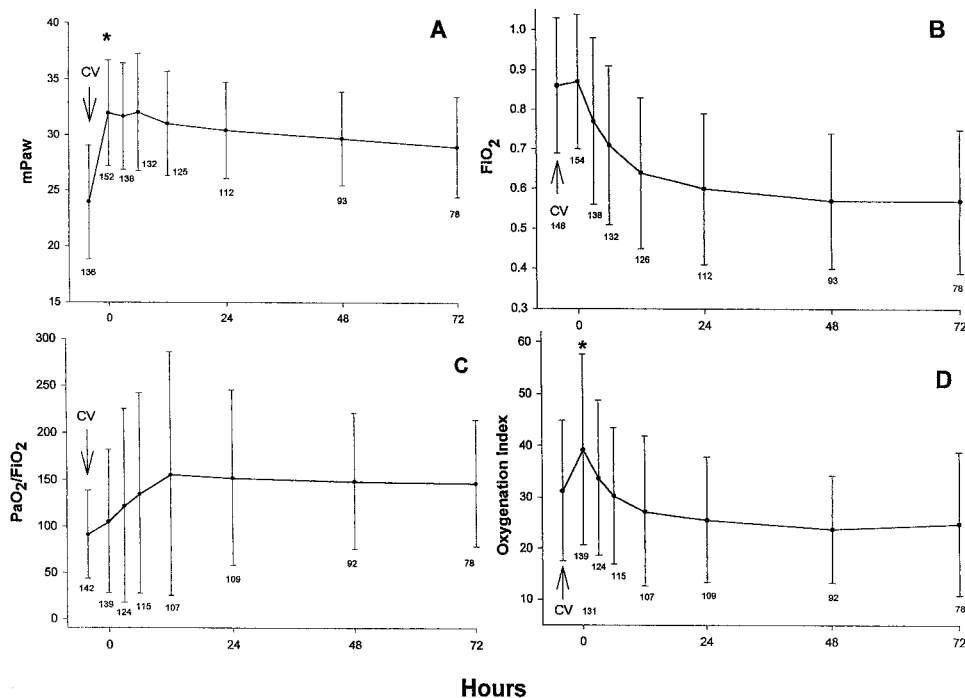


FIGURE 1. mPaw (top left, A), FIO₂ (top right, B), PaO₂/FIO₂ ratio (bottom left, C), and OI (bottom left, D) plotted over the study duration. CV represents values observed during CV immediately prior to initiating HFOV therapy. All subsequent measurements were made during HFOV therapy. Time 0 represents values observed within 30 min of HFOV initiation. Values are given as the mean ± SD. The numbers adjacent to each data point represent the number of trials. The p values for trends in physiologic parameters are as follows: mPaw, p < 0.001; FIO₂, p < 0.001; PaO₂/FIO₂ ratio, p = 0.0002; OI, p < 0.0001 (all by repeated-measures analysis of variance).

pressure amplitude of oscillation (*ie*, 71 ± 17 to 65 ± 16 cm H₂O; p = 0.002) and frequency (4.7 ± 1.0 to 5.2 ± 1.8 Hz; p = 0.048). mPaw declined from 30.8 ± 5.7 cm H₂O on HFOV initiation to 23.9 ± 5.3 prior to transition to CV (p < 0.0001), to 21.0 ± 4.6 immediately following the transition to CV (p < 0.0001 [compared with pretransition mPaw]). There were no significant changes in gas exchange or hemodynamics with the transition to CV.

Forty-one patients (26%) had therapy with HFOV discontinued due to difficulties with oxygenation, ventilation, or hemodynamics. Their median duration of HFOV was 18.6 h (range, 0 to 668 h). Nineteen of these patients (12%) had therapy with HFOV discontinued within 4 h. Compared with other patients, these 19 had lower baseline pH values (7.19) ± 0.13 vs 7.29 ± 0.11, respectively; p = .001), higher baseline OI (37.8 ± 15.8 vs 30.3 ± 0.13, respectively; p = 0.03), and higher mortality rate (90% vs 57%, respectively; p = 0.11).

Patient Outcomes With HFOV

Patient outcomes and the use of concomitant therapies for ARDS such as inhaled nitric oxide

(NO) are presented in Table 2. The median duration of HFOV therapy in all patients was 3.5 days (25 to 75% CI, 0.8 to 6.8 days). Neuromuscular blocking agents were administered continuously during HFOV therapy to 90% of patients. Twenty-one percent of patients exhibited spontaneous respirations at some time during HFOV therapy. At 30 days, the mortality rate was 61.7%. Of the survivors, approximately half still required ventilatory support. The mortality rate remained constant throughout the 4 years.

Survivors vs Nonsurvivors

Table 3 shows the baseline characteristics of survivors and nonsurvivors prior to receiving HFOV therapy. Nonsurvivors were significantly older, had higher APACHE II scores and multiple organ dysfunction scores (MODSs), were more likely to be immunocompromised, had ARDS longer, and received CV for a greater number of days prior to receiving HFOV therapy. Baseline pH was lower and peak inspiratory pressure during CV was higher in nonsurvivors. The total duration of ventilation was greater in survivors.

Figure 3 illustrates the temporal course of PaO₂/

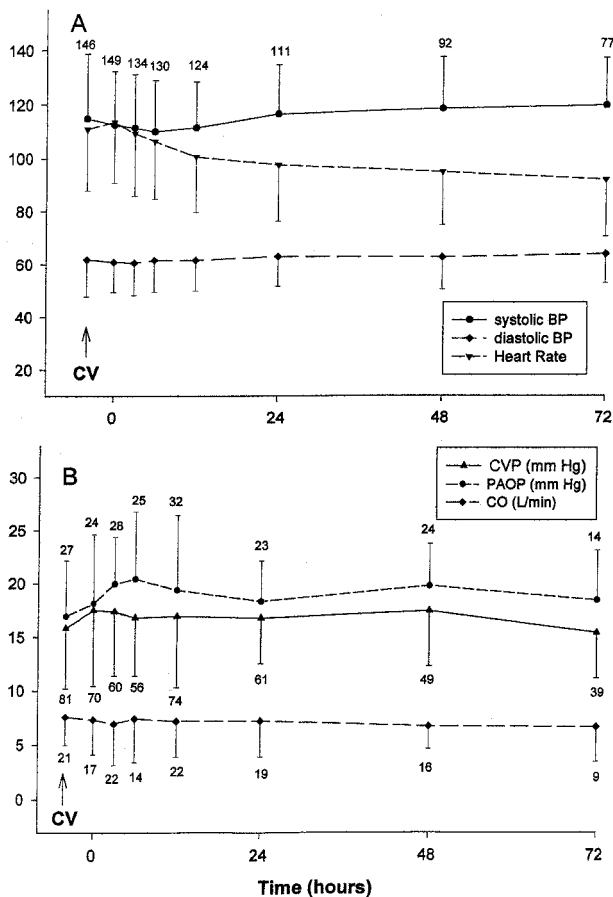


FIGURE 2. Systolic BP, diastolic BP, and heart rate (top, A), and CVP, PAOP, and CO (bottom, B) plotted over the duration of the study. CV represents values observed during CV immediately prior to initiating HFOV therapy. All subsequent measurements were made during HFOV therapy. Time 0 represents values observed within 30 min of HFOV initiation. Values are given as the mean \pm SD. The numbers adjacent to each data point represent the number of trials. The p values for trends in physiologic parameters are as follows: systolic BP, $p = 0.03$; heart rate, $p < 0.0001$; CVP, $p = 0.01$; CO, $p = 0.004$.

FI_{O_2} ratio, OI, FI_{O_2} , and $PaCO_2$ after the initiation of HFOV therapy in both survivors and nonsurvivors. $mPaw$ was similar in survivors and nonsurvivors throughout the 72 h (data not shown). PaO_2/FI_{O_2} ratio was higher and OI was lower in survivors ($p = 0.018$ vs $p = 0.001$, respectively). FI_{O_2} could be reduced with the application of HFOV therapy in both groups, but survivors required lower FI_{O_2} values than did nonsurvivors ($p < 0.0001$). There was no difference in $PaCO_2$ between the two groups.

Predictors of Outcome

Multivariate analysis identified the following four baseline parameters that significantly predicted the 30-day mortality rate (Table 4): age ($p = 0.0341$); APACHE II score at ICU admission ($p = 0.0317$);

Table 2—Patient Outcomes Using HFOV*

Outcomes	Values
Duration of HFOV, d	5.1 \pm 6.3
Pneumothorax during HFOV	34 (21.8)
Reason for withdrawal of HFOV	
Successfully weaned	76 (48.7)
Withdrawal of life support/death	38 (24.4)
Technical problem	5 (3.2)
Oxygenation difficulty	12 (7.7)
Ventilation difficulty	23 (14.7)
Hemodynamic instability	8 (5.1)
Other therapies	
INO	68 (43.6)
Steroids	58 (37.2)
Prone positioning	10 (6.4)
HFJV	5 (3.2)
ECMO	2 (1.2)
Outcome at 30 d	
Died	95 (61.7)
Alive	
No ventilatory support	28 (18.2)
Ventilated	31 (20.1)

*Values given as means \pm SD or No. (%). HFJV = high-frequency jet ventilation; ECMO = extracorporeal membrane oxygenation.

number of CV days prior to starting HFOV therapy ($p = 0.0115$); and baseline pH ($p = 0.0083$). Stepwise logistic regression identified OI as the most significant posttreatment predictor of mortality and OI at 24 h as the most significant time point ($p = 0.0066$). The relationship between predicted mortality and OI at 24 h, controlling for baseline conditions, is shown in Figure 4.

We identified an OI of < 15 at 24 h or an improvement of at least 30% in the OI at > 24 h as the best dichotomous criteria for survival (sensitivity, 0.63; specificity, 0.67; $p = 0.007$).

DISCUSSION

The purpose of the current study was to summarize the experience with HFOV therapy in three Toronto medical/surgical ICUs. We observed the following. First, HFOV is used as rescue therapy in adults with ARDS due to a wide variety of etiologies, when patients are already requiring high FI_{O_2} and/or high airway pressures. Second, the use of HFOV is associated with improvements in ventilation and oxygenation, the latter permitting significant reductions in delivered FI_{O_2} . Third, 26% of patients had HFOV therapy discontinued due to difficulties with oxygenation, ventilation, or hemodynamics. Fourth, the incidence of pneumothorax is higher in this population than in other reported ARDS patients.^{19–21} Fifth, compared with survivors, nonsurvivors are older, have higher severity of illness,

Table 3—Patient Characteristics in the Three ICUs*

Characteristics	MSH (n = 75)	SWCHSC (n = 29)	UHN (n = 52)
Age, yr	48 ± 19	41 ± 19	50 ± 16
Sex, % female	43	31	50
ARDS etiology, %			
Sepsis	65	50	58
Pulmonary infection	16	35	12
Trauma	0	12	0
Other	19	4	31
APACHE II score in 1st 24 h in ICU	26.4 ± 7.4	18.0 ± 6.0	23.0 ± 6.6
Immunocompromised patients†, %	37.3	7.4	36.5
LIS	3.5 ± 0.4	3.2 ± 0.5	3.6 ± 0.3
ARDS prior to HFOV, d	4.3 ± 5.4	2.9 ± 3.0	2.8 ± 3.0
Ventilation prior to HFOV, d	5.3 ± 8.8	8.1 ± 7.0	4.7 ± 5.5
Duration of HFOV, d	6.4 ± 7.2	4.3 ± 3.9	3.6 ± 5.0
Total duration of MV, d	19.7 ± 20	23.8 ± 15.1	23.5 ± 22.7
Outcome at 30 d, %			
Died	60.8	50.0	69.2
Alive			
No ventilatory support	13.5	17.9	3.8
Ventilated	25.7	32.1	26.9

*Values given as means ± SD, unless otherwise indicated. MSH = Mount Sinai Hospital; SWCHSC = Sunnybrook & Women's College Health Sciences Center; UHN = University Health Network; MV = mechanical ventilation.

†Bone marrow or solid organ transplant, malignancy, AIDS, steroids, for example.

require higher peak pressures during CV, and have received CV for a greater number of days prior to receiving HFOV therapy.

Our findings are similar to those of previous observational trials^{12,13,16} and those of one randomized controlled trial,¹⁷ showing that HFOV therapy is a safe and effective mode of ventilation in the treatment of ARDS in adults. The observational studies^{12,13,16} reported improvements in oxygenation and adequate ventilation in adults with severe ARDS treated with HFOV. Two of these trials^{12,13} identified the fact that a greater number of pretreatment days receiving CV was significantly associated with mortality. In both studies, the 30-day mortality rates were quite high (Fort et al,¹² 53%; Mehta et al,¹³ 67%). However, HFOV was applied as rescue therapy to patients requiring high FIO₂ and/or ventilatory pressures, and deaths were due to multiple organ failure, not to hypoxemia.

There is only one randomized trial evaluating HFOV in adults.¹⁷ In this multicenter trial, 148 adults with ARDS were randomized to CV or HFOV. The HFOV group showed early improvement in PaO₂/FIO₂ ratio compared with the conventional group, however, the difference did not persist beyond 24 h. The 30-day mortality rate was 37% in the HFOV group, and 52% in the CV group (p = 0.102). There were no significant differences in hemodynamic variables, oxygenation failure, ventilation failure, or barotrauma between the two groups.

The 30-day mortality rate in the current study was 61.7%, which is higher than those in the studies by

Fort et al¹² and Derdak et al,¹⁷ despite similar APACHE II scores. The higher mortality rate in the current study may relate to patient parameters that are not captured in the APACHE II score, such as burn injury or organ/bone marrow transplantation.

Hemodynamics

The higher mPaw applied during HFOV therapy was associated with an early and nonpersistent increase in PAOP, a small persistent increase in CVP, and a small decrease in CO. The increase in PAOP and CVP likely is related to changes in cardiac transmural pressure during HFOV therapy, however, without direct measurements of intrathoracic pressure, we cannot confirm this. These findings are very similar to those of three previous studies,^{12,13,17} which also reported an early rise in CVP and/or PAOP, while Mehta and colleagues¹³ observed a significant reduction in CO with the application of HFOV. Two pediatric studies^{22,23} also found significant reductions in CO measured noninvasively in infants converted from CV to HFOV.

The clinical significance of these hemodynamic effects is not known, as we do not have data on fluid or vasopressor administration at the time of HFOV initiation. However, the CO remained within a normal range throughout the study period, and the HFOV-induced reduction in CO was not associated with a drop in BP or a rise in heart rate. In addition, although lactate levels were not measured, patients did not develop worsening acidosis.

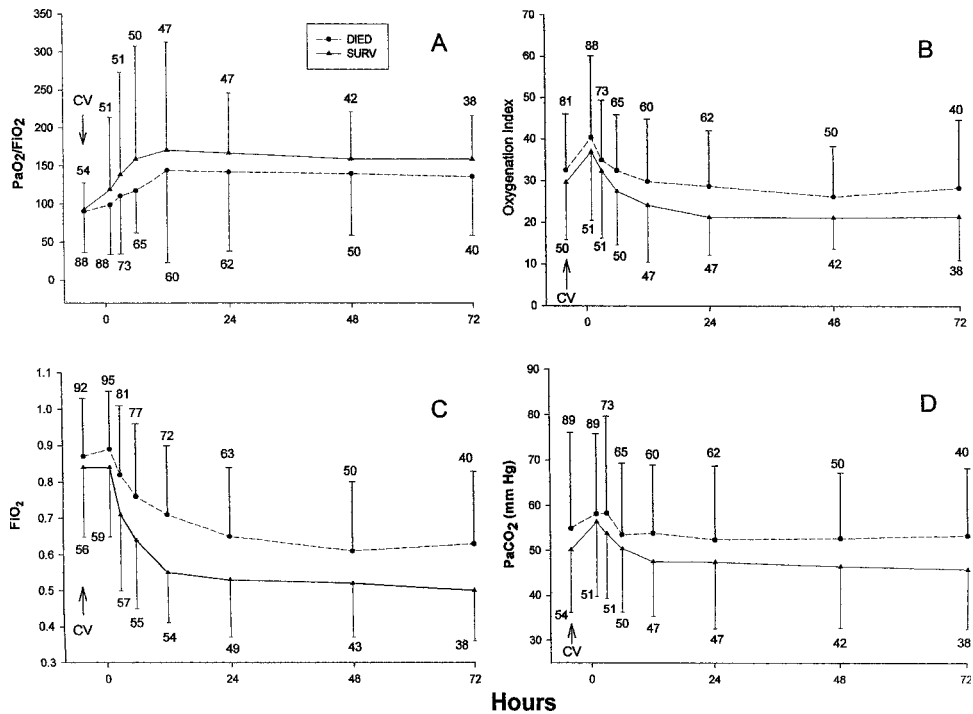


FIGURE 3. PaO_2/FIO_2 ratio (top left, A), OI (top right, B), FIO_2 (bottom left, C), and $PaCO_2$ (bottom right, D) in survivors (SURV) and nonsurvivors (DIED) plotted over the study duration. CV represents values observed during CV immediately prior to initiating HFOV therapy. All subsequent measurements were made during HFOV therapy. Time 0 represents values observed within 30 min of HFOV initiation. Values are given as the mean \pm SD. The numbers adjacent to each data point represent the number of trials. The p values represent the difference between survivors and nonsurvivors over the 3 days, as follows: PaO_2/FIO_2 ratio, $p = 0.018$; OI, $p = 0.001$; CVP, $p < 0.0001$; $PaCO_2$, p value not significant.

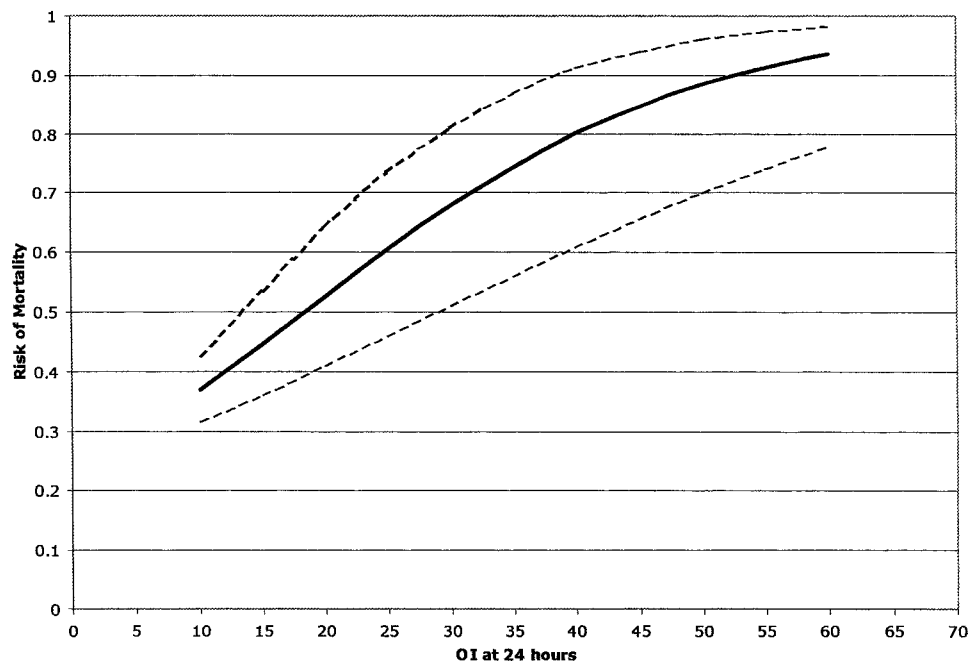


FIGURE 4. The relationship between predicted mortality and OI at 24 h, controlling for baseline conditions. The interrupted lines indicate the upper and lower 95% CIs.

Complications

Overall, 26% of patients did not tolerate HFOV therapy and were returned to CV because of difficulties with oxygenation, ventilation, or hemodynamics. Twelve percent of patients had HFOV therapy discontinued within 4 h. These patients had lower pH values, higher OI values, and higher mortality rates than those patients who had no difficulties tolerating HFOV therapy. There are many possible explanations for the lack of response to HFOV, including hypovolemia, poor cardiac function, or the presence of a poorly recruitable lung.

The observed pneumothorax rate (21.8%) is higher than the rates observed in studies^{20,21,24} evaluating conventional treatment strategies in adults with ARDS, in which barotrauma rates ranged from 7 to 14%. Derdak and colleagues¹⁷ reported pneumothorax rates of 9% and 12%, respectively, in the HFOV and CV groups. The higher rate in the

current study was likely due to the patients' severity of illness. Another possible explanation relates to differences in HFOV utilization and settings. However, this explanation is not likely, since the applied mPaw was not higher in the current study than those used in previous studies evaluating HFOV,^{12,13,16,17} and there was no difference in the pneumothorax rate among the three ICUs.

HFOV Combined With Other Therapies

In the current study, 66.7% of patients were treated with inhaled NO, steroids, or prone positioning during HFOV. One small randomized trial²⁵ found that methylprednisolone given to patients with unresolving ARDS was associated with reduced mortality. However, prospective trials^{26,27} have failed to show any mortality benefit of NO or prone positioning in patients with ARDS. Nonetheless, clinicians

Table 4—Characteristics of Survivors and Nonsurvivors*

Characteristics	Survivors (n = 59)	Nonsurvivors (n = 95)	p Value
Age, yr	42.4 ± 16.3	51.3 ± 19.0	0.0026
Sex, %			
Male	48	62	
Female	52	38	
APACHE II			
1st 24 h in ICU	21.5 ± 7.4	25.3 ± 7.3	0.0028
24 h prior to HFOV	21.0 ± 8.2	25.8 ± 7.2	0.0006
MODS	8.5 ± 3.2	8.9 ± 3.8	0.0486
Immunocompromised,† %	20.3	39.4	
LIS‡	3.5 ± 0.4	3.5 ± 0.4	
ARDS prior to HFOV, d	2.9 ± 3.1	4.0 ± 4.9	
Ventilation prior to HFOV, d	4.4 ± 5.2	6.5 ± 8.7	0.0113
Gas exchange prior to HFOV			
pH	7.33 ± .10	7.25 ± .12	< 0.0001
PaCO ₂ , mm Hg	50.2 ± 14.1	55.0 ± 21.2	
PaO ₂ /FiO ₂ , mm Hg	92.6 ± 34.8	90.4 ± 54.4	
OI§	29.6 ± 13.8	32.5 ± 13.5	
Pulmonary artery catheter, No.	16 (27%)	16 (17%)	
Ventilator parameters during CV			
Plateau pressure, cm H ₂ O	34.2 ± 6.5	37.3 ± 6.3	0.0065
PEEP, cm H ₂ O	14.3 ± 2.8	13.8 ± 3.4	
mPaw, cm H ₂ O	24.0 ± 6.0	24.1 ± 4.4	
FiO ₂	0.84 ± 0.19	0.87 ± 0.16	
Air leak prior to HFOV, %	28.8	30.5	
New air leak during HFOV, %	22.0	22.1	
Other therapies, No.			
INO	22 (37.2%)	46 (48.4%)	
Steroids	23 (39.0%)	35 (36.8%)	
Prone positioning	6 (10.1%)	4 (4.2%)	
HFJV	1 (1.7%)	4 (4.2%)	
Duration of HFOV, d	6.8 ± 6.7	4.1 ± 5.6	< 0.0001
Total duration of MV, d	34.8 ± 23.4	12.5 ± 10.1	

*Values given as mean ± SD, unless otherwise indicated. See Tables 1 through 3 for abbreviations not used in the text.

†Bone marrow transplant, malignancy, AIDS, steroids, for example.

‡Data from Murray et al.¹⁹

§OI = FiO₂ × mPaw × 100/PaO₂.

||Survivors, 38 patients; Nonsurvivors, 69 patients.

continue to use these latter measures in desperation, since individual patients may show improvements in oxygenation.²⁸

The physiologic rationale for the combined use of HFOV and NO is sound. Alveolar recruitment during HFOV may increase the amount of alveolar/capillary interface available for inhaled NO (INO) to act on, potentially resulting in greater improvements in ventilation-perfusion matching than those achieved with each individual therapy. In a prospective study¹⁸ evaluating the combined use of HFOV and NO, 83% of patients demonstrated at least a 20% improvement in PaO₂/FIO₂ ratio, with an average improvement of 38%. In addition, the use of INO allowed significant reductions in FIO₂ within 8 to 12 h.¹⁸ Despite physiologic benefit, there is no evidence that therapy with HFOV, INO, or both in combination reduces mortality in adults with ARDS.

Predictors of Mortality

Multivariate analysis identified OI at 24 h after HFOV initiation as the most significant posttreatment predictor of mortality. Derdak and colleagues¹⁷ also identified OI trend as the most significant posttreatment predictor of survival regardless of assigned ventilator, with the 16-h OI as the most discriminating time point. Fort and colleagues¹² identified the fact that an OI of > 47 predicted mortality with a sensitivity and specificity of 100%. In a large retrospective assessment of HFOV therapy in 10 pediatric ICUs, OI at 24 h also was found to be an important predictor of survival.²⁹ We found that a 24-h OI of ≤ 15 or a 30% improvement in OI at > 24 h was a reasonable predictor of survival, but that it was not as significant as the continuous OI value. In the ARDS population, with such an array of confounding risk factors, multivariate models may be more helpful than a single variable in predicting mortality. Nevertheless, OI may serve as an additional indicator of the probability of survival.

Four other parameters also significantly predicted 30-day mortality in our population, as follows: age; APACHE II score; number of days receiving CV prior to receiving HFOV; and baseline pH. Three previous studies^{12,13,17} also identified that a greater number of pretreatment CV days correlated directly with mortality. This observation from multiple studies highlights the importance of developing criteria for the early initiation of HFOV as rescue therapy.

CONCLUSION

The major limitation of our report is its retrospective nature. There was no standard protocol for HFOV initiation or titration, sedation, neuromuscu-

lar blockade, fluid administration, or vasopressor therapy. As such, practices varied among institutions. In addition, HFOV therapy was used primarily in a medical population.

HFOV has become the standard of care for the treatment of neonatal respiratory distress syndrome. Support for the use of HFOV therapy in adults with ARDS is more limited and awaits the performance of rigorous trials comparing HFOV to CV using low tidal volumes, evaluating outcomes such as mortality. Until then, HFOV therapy shows promise as rescue therapy to improve oxygenation in patients not responding to conventional therapy.

ACKNOWLEDGMENT: The authors wish to thank Sensor-Medics for partial support.

REFERENCES

- 1 Krishnan JA, Brower RG. High-frequency ventilation for acute lung injury and ARDS. *Chest* 2000; 118:795–807
- 2 Hamilton PP, Onayemi A, Smyth JA et al. Comparison of high-frequency ventilation: oxygenation and lung pathology. *J Appl Physiol* 1983; 55:131–138
- 3 McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant deficient rabbits. *Am Rev Respir Dis* 1988; 137:1185–1192
- 4 Coalson JJ, deLemos RA. Pathologic features of various ventilatory strategies. *Acta Anaesthesiol Scand Suppl* 1989; 90:108–116
- 5 Yoder BA, Siler-Khodr T, Winter VT, et al. High-frequency oscillatory ventilation: effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. *Am J Respir Crit Care Med* 2000; 162:1867–1876
- 6 Imai Y, Kawano T, Miyasaka K, et al. Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation. *Am J Respir Crit Care Med* 1994; 150:1550–1554
- 7 Imai Y, Nakagawa S, Ito Y, et al. Comparison of lung protective strategies using conventional and high-frequency oscillatory ventilation. *J Appl Physiol* 2001; 91:1836–1844
- 8 Arnold JH, Hanson JH, Toro-Figuero LO, et al. Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 1994; 22:1530–1539
- 9 Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics* 1996; 98:1044–1057
- 10 Plavka R, Kopecky P, Sebron V, et al. A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome. *Intensive Care Med* 1999; 25:68–75
- 11 Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med* 2002; 347:643–652
- 12 Fort P, Farmer C, Westerman J, et al. High-frequency oscillatory ventilation for adult respiratory distress syndrome: a pilot study. *Crit Care Med* 1997; 25:937–947
- 13 Mehta S, Lapinsky SE, Hallet DC, et al. A prospective trial of

- high frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2001; 29:1360–1369
- 14 Claridge JA, Hostetter RG, Lawson SM, et al. High-frequency oscillatory ventilation can be effective as rescue therapy for refractory acute lung dysfunction. *Am Surg* 1999; 65:1092–1096
 - 15 Cartotto R, Cooper AB, Esmond JR, et al. Early clinical experience with high-frequency oscillatory ventilation for ARDS in adult burn patients. *J Burn Care Rehabil* 2001; 22:325–333
 - 16 Andersen FA, Guttormsen AB, Flaatten HK. High frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome: a retrospective study. *Acta Anaesthesiol Scand* 2002; 36:1082–1088
 - 17 Derdak S, Mehta S, Stewart TE, et al. High frequency oscillatory ventilation for acute respiratory distress syndrome in adults. *Am J Respir Crit Care Med* 2002; 166:801–808
 - 18 Mehta S, MacDonald R, Hallett D, et al. Acute oxygenation response to inhaled nitric oxide (INO) when combined with high frequency oscillatory ventilation (HFOV) in adults with the acute respiratory distress syndrome. *Crit Care Med* 2003; 31:383–389
 - 19 Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138:720–723
 - 20 Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355–361
 - 21 Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:1831–1838
 - 22 Laubscher B, van Melle G, Fawer CL, et al. Haemodynamic changes during high frequency oscillation for respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 1996; 74:F172–F176
 - 23 Simma B, Fritz M, Fink C, et al. Conventional ventilation versus high-frequency oscillation: hemodynamic effects in newborn babies. *Crit Care Med* 2000; 28:227–231
 - 24 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
 - 25 Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998; 280:159–165
 - 26 Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial; Inhaled Nitric Oxide in ARDS Study Group. *Crit Care Med* 1998; 26:15–23
 - 27 Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573
 - 28 Varkul MD, Stewart TE, Lapinsky SE, et al. Successful use of combined high frequency oscillatory ventilation, inhaled nitric oxide, and prone positioning in the acute respiratory distress syndrome. *Anesthesiology* 2001; 95:797–799
 - 29 Arnold JH, Anas NG, Luckett P, et al. High-frequency oscillatory ventilation in pediatric respiratory failure: a multicenter experience. *Crit Care Med* 2000; 28:3913–3919