

Feature Article

Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure

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Objective: To compare the effectiveness of high-frequency oscillatory ventilation with conventional mechanical ventilation in pediatric patients with respiratory failure.

Setting: Five tertiary care pediatric intensive care units.

Design: A prospective, randomized, clinical study with crossover.

Patients: Seventy patients with either diffuse alveolar disease and/or airleak syndrome were randomized to receive high-frequency oscillatory ventilation or conventional mechanical ventilation.

Interventions: Patients randomized to receive high-frequency oscillatory ventilation were managed, using a strategy that consisted of aggressive increases in mean airway pressure to attain the "ideal" lung volume and to achieve an arterial oxygen saturation of $\geq 90\%$, with an FIO_2 of ≤ 0.6 . Patients who were randomized to receive conventional mechanical ventilation were treated with a strategy that utilized increases in end-expiratory pressure and inspiratory time to increase mean airway pressure and to limit increases in peak inspiratory pressure. Target blood gas values were the same for both

groups. Crossover to the alternate ventilator was required if the patient met defined criteria for treatment failure.

Measurements and Main Results: Physiologic data and ventilatory parameters were collected prospectively at predetermined intervals after randomization. Airleak Scores were derived daily, based on the chest radiograph and the patient's clinical condition. In the high-frequency oscillatory ventilation group, the $\text{PaO}_2/\text{PAO}_2$ ratio increased significantly and the oxygenation index (mean airway pressure $\times \text{FIO}_2 \times 100/\text{PaO}_2$) decreased significantly over time. There were no differences between the groups in duration of mechanical ventilation, frequency of airleak, Airleak Scores, or 30-day survival rates. Significantly fewer patients treated with high-frequency oscillatory ventilation required supplemental oxygenation at 30 days compared with patients managed with conventional ventilation. When ventilatory subgroups were compared, the patients managed with high-frequency oscillation only had significantly better ranked outcomes than patients managed with conventional ventilation only.

Conclusions: Our results indicate that high-frequency oscillatory ventilation, utilizing an aggressive volume recruitment strategy, results in significant improvement in oxygenation compared with a conventional ventilatory strategy designed to limit increases in peak airway pressures. Furthermore, despite the use of higher mean airway pressures, the optimal lung volume strategy used in this study was associated with a lower frequency of barotrauma, as indicated by requirement for supplemental oxygen at 30 days, and improved outcome compared with conventional mechanical ventilation. (Crit Care Med 1994; 22:1530-1539)

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KEY WORDS: adult respiratory distress syndrome; high-frequency ventilation; intermittent positive-pressure ventilation; mechanical ventilation; pediatrics; respiration; respiration, artificial; respiration disorders; respiratory distress syndrome; respiratory insufficiency; ventilators, mechanical

High-frequency oscillatory ventilation has been shown to decrease the frequency of chronic lung disease compared with conventional mechanical ventilation in preterm infants with hyaline membrane disease (1, 2). In several centers, high-frequency oscillatory ventilation has proven to be a valuable ventilatory alternative in newborn infants who meet criteria for extracorporeal membrane oxygenation (3–5). We (6, 7) previously described our experience with high-frequency oscillatory ventilation as a rescue technique in pediatric patients with diffuse alveolar disease and airleak syndromes and demonstrated high-frequency oscillatory ventilation to be a safe and effective ventilatory alternative.

We hypothesized that pediatric patients with respiratory failure would respond to high-frequency oscillation with immediate and sustained improvement in oxygenation. By utilizing an aggressive strategy to recruit and maintain the "ideal" lung volume, we hoped to improve gas exchange while minimizing the degree of ventilator-induced lung injury. We report the results of a multicenter, prospective, randomized trial comparing high-frequency oscillatory ventilation with conventional mechanical ventilation in pediatric patients with diffuse alveolar disease and/or airleak.

MATERIALS AND METHODS

Entry Criteria. This study includes patients from five tertiary care, pediatric intensive care units: Children's Hospital, Boston, MA; Children's Hospital, Oakland, CA; Children's Medical Center, Dallas, TX; Children's Hospital of Wisconsin, Milwaukee, WI; and Children's Hospital, Columbus, OH. The study protocol was approved by the Institutional Review Board of each institution.

Patients meeting the following entry criteria were considered eligible for participation in the study.

- a) Body weight of ≤ 35 kg.
- b) One or both of the following nonexclusive diagnostic categories: acute diffuse lung injury (acute hypoxic respiratory failure), associated with poor or decreased lung compliance, resulting in respiratory failure and the need for mechanical ventilatory support with positive airway pressure; pulmonary barotrauma greater than grade 1 in severity (Appendix).
- c) One or both of the following measurable conditions: oxygenation index of >13 (mean airway pressure $\times \text{FiO}_2 \times 100/\text{PaO}_2$), demonstrated by two consecutive arterial blood gas measurements over a 6-hr period; radiographic evidence of barotrauma, as defined above.
- d) Patient representative willing to sign informed consent for randomization into the study.

Exclusions. The following patients and/or patient conditions were specifically excluded: a) infants <40 wks postconceptual age or former prematurity with residual chronic lung disease; b) obstructive airway disease, including bronchiolitis, asthma, cystic fibrosis, and bronchopulmonary dysplasia, with clinical evidence of increased expiratory resistance (e.g.,

Appendix. Study definitions

Gross Airleak Score: Airleak Scores were recorded after daily review of the patient's chest radiograph by a radiologist blinded to the mode of ventilation, using the following scoring system:

- Grade 0: No airleak
- Grade 1: Isolated pneumomediastinum without tension
- Grade 2: Uni- or bilateral pneumothorax, requiring only a single chest tube per hemithorax; no recurrences; airleak stops within 72 hrs; with or without pneumomediastinum
- Grade 2S: Surgically induced airleak (e.g., after open-lung biopsy)
- Grade 3: Return of pneumothorax, requiring additional chest tubes or replacement/repositioning of existing chest tubes (≤ 4 occurrences); or airleak continuing for 72 to 120 hrs
- Grade 4: Unstable airleak, with multiple recurrent episodes (>4); or airleak requiring more than two chest tubes per hemithorax; or airleak continuing for >120 hrs; or pneumopericardium or pneumoperitoneum (due to pulmonary airleak)

Intractable Shock: Intractable shock is defined as the presence of one of the following conditions in a patient with adequate preload (defined by a central venous pressure of >15 mm Hg or pulmonary artery occlusion pressure of >20 mm Hg):

- a) Mean arterial pressure of >2 SD below normal (20)
- b) Inotropic support of >20 $\mu\text{g}/\text{kg}/\text{min}$ of dopamine and dobutamine or equivalent
- c) Cardiac index of <2.6 $\text{L}/\text{min}/\text{m}^2$

If any such patients recovered from intractable shock and became hemodynamically stable, they were considered eligible for participation in the study.

wheezing or hyperinflation on chest radiograph); c) intractable septic or cardiogenic shock (Appendix); d) nonpulmonary terminal diagnosis.

Enrollment and Randomization. Patients meeting the entry criteria were randomized to receive either high-frequency oscillation or conventional mechanical ventilation, using a stratified, balanced-block randomization procedure designed to ensure equal numbers of patients with diffuse lung injury and pulmonary barotrauma in each ventilatory group at each study site. Data collected before entry into the study included a physical examination by a study physician, ventilatory hours at the time of randomization, FIO_2 , mean airway pressure, peak airway pressure, end-expiratory pressure, arterial blood gas analysis, systolic and diastolic blood pressure, heart rate, current medications, and Pediatric Risk of Mortality score (8).

High-Frequency Oscillation Strategy: Diffuse Alveolar Disease. Patients randomized to receive high-frequency oscillatory ventilation were managed, using an aggressive strategy designed to rapidly recruit and maintain optimal lung volume, which has been previously described (6). The high-frequency device used in this study was a piston-driven device that offers an active expiratory phase, a variable inspiration/expiration ratio, a well-humidified continuous bias flow, and an operating frequency between 3 and 15 Hz (3100, SensorMedics, Yorba Linda, CA). Initial oscillator settings were standardized according to the following parameters: FIO_2 1.0; operating frequency 5 to 10 Hz; inspiratory time 33%; mean airway pressure 4 to 8 $\text{cm H}_2\text{O}$ greater than previously required on conventional ventilation; bias gas flow of $\geq 18 \text{ L/min}$; and pressure amplitude adjusted to provide adequate chest wall movement.

Management of persistent hypoxemia in patients with adequate cardiac performance and no radiographic signs of lung overinflation was directed at increasing lung volume. The mean airway pressure was increased by 1- to 2-cm H_2O increments until arterial oxygen saturation was $\geq 90\%$ with an FIO_2 of ≤ 0.6 or until the chest radiograph showed hyperinflation. Lung hyperinflation was identified using regular chest radiography and was defined as the presence of both flattened diaphragms and more than nine ribs (posterior) of lung expansion.

Management of hypoxemia in patients with demonstrated or suspected cardiac dysfunction was directed at optimizing preload and contractile function. Invasive monitoring, including pulmonary artery catheterization and measurement of thermodilution cardiac output, was used, when indicated, to assess the hemodynamic consequences of high-frequency oscillation and to ensure preservation of oxygen delivery. In

patients who demonstrated adverse hemodynamic responses to high-frequency oscillation, aggressive volume expansion was attempted to achieve adequate preload. Adequate preload was defined as a central venous pressure of $>15 \text{ mm Hg}$ or a pulmonary artery occlusion pressure of $>20 \text{ mm Hg}$. Inotropic support was provided with dopamine and dobutamine once preload was optimized.

The initial pressure amplitude was selected on the basis of adequate chest wall movement by subjective impression and/or objective monitoring of transcutaneous PCO_2 . The transcutaneous CO_2 sensor (840, Novametrics Medical Systems, Wallingford, CT) was placed on a well-perfused site on the chest or abdomen, ~ 20 mins before initiation of high-frequency oscillation, in order to ensure a stable baseline and reliable responsiveness to changes in PCO_2 . The target PCO_2 was between 45 and 55 torr (6.0 and 7.3 kPa), although as long as the arterial pH was >7.25 , higher PCO_2 values were tolerated. If adequate ventilation could not be achieved with the maximum pressure amplitude, the oscillatory frequency was incrementally decreased by 1 to 2 Hz to a minimum of 3 Hz, as oscillatory tidal volume is inversely related to ventilatory frequency during high-frequency oscillation with this device.

During high-frequency oscillation, patients were routinely paralyzed using a nondepolarizing muscle relaxant and were sedated using an opioid/benzodiazepine combination, as our initial experience (6) suggested that spontaneous ventilation during high-frequency oscillation in this patient population was uniformly unsuccessful. Once adequate oxygenation (arterial oxygen saturation $\geq 90\%$) was achieved with an FIO_2 of ≤ 0.6 , mean airway pressure was decreased in 1- to 2-cm increments. In general, patients were preoxygenated with an FIO_2 of 1.0 and were then removed from the oscillator during endotracheal suctioning. When the patient tolerated endotracheal suctioning without significant changes in saturation after reinstitution of high-frequency oscillation and the mean airway pressure was $18 \pm 3 \text{ cm H}_2\text{O}$, conventional mechanical ventilation was reinstated. If adequate oxygenation (arterial oxygen saturation of $\geq 90\%$ with an FIO_2 of ≤ 0.35 and mean airway pressure of $<15 \text{ cm H}_2\text{O}$) and ventilation (pH of >7.25 , with ventilatory rate of <30 breaths/min, peak inspiratory pressure of $<35 \text{ cm H}_2\text{O}$) could be maintained, the patient was considered to have been successfully weaned to conventional ventilation. When the study investigators felt that a trial of spontaneous ventilation was appropriate, patients were slowly weaned from muscle relaxants and sedatives, as tolerated.

Conventional Mechanical Ventilation Strategy: Diffuse Alveolar Disease. Patients treated with

conventional ventilation were managed, using a strategy that utilized increases in end-expiratory pressure and inspiratory time to increase mean airway pressure and limit increases in peak inspiratory pressure. The ventilators utilized in this group included the Servo 900C® (Siemens, Solna, Sweden) and the Veolar® (Hamilton Medical, Reno, NV). Target blood gas values were the same as for high-frequency oscillation, with an FIO_2 to be kept at <0.6 throughout therapy. Management of persistent hypoxemia in patients with good cardiac performance and no radiographic signs of lung overinflation was directed at increasing lung inflation. The end-expiratory pressure was increased by 2- to 4-cm increments until oxygenation was improved or until there were signs of compromised cardiac function. Management of persistent hypoxemia in patients with signs of poor cardiac performance was directed at improving cardiac performance (as described above for the high-frequency oscillation group). In patients who responded to conventional ventilation with improvement in oxygenation, decreases in FIO_2 (until FIO_2 was <0.60) took priority over decreasing the end-expiratory pressure, as long as the lung fields were not overinflated. The target PCO_2 was between 45 and 55 torr (6.0 and 7.3 kPa), although as long as the arterial pH was >7.25, higher PCO_2 values were tolerated. Hypercarbia was managed by increasing the ventilatory rate when the patient had good lung inflation. The quality of lung inflation was based on chest radiograph, tidal volume delivery, and chest wall movement. Hypercarbia was managed by increasing the tidal volume when lung inflation and tidal volume delivery were inadequate (according to chest radiograph and chest wall movement). In patients with hypercarbia and lung hyperinflation, the adverse effects of excessive or inadvertent positive end-expiratory pressure were assessed and decreases in end-expiratory pressures or rates were made appropriately. The administration of muscle relaxants and intravenous sedatives was left to the judgment of the study investigators at each study site.

High-Frequency Oscillation and Conventional Ventilation Strategy: Airleak Syndrome. Initial management of patients with airleak was identical to the management strategy described for patients with diffuse alveolar disease. We began high-frequency oscillatory ventilation or conventional mechanical ventilation in patients with primary diagnoses of airleak by defining the lung volume at which the most efficient oxygen delivery occurred. Once adequate oxygenation was achieved (arterial oxygen saturation of ≥90%, with an FIO_2 of ≤0.6), an attempt was made to limit airway pressure by aggressively decreasing either mean airway pressure and pressure amplitude (high-

frequency oscillation) or peak inspiratory pressure (conventional ventilation) over 12 to 24 hrs. During this period, adequate oxygenation (arterial oxygen saturation of 85% to 90%) was maintained, with incremental increases in FIO_2 , if necessary. Hypercarbia was tolerated as long as the arterial pH was >7.25. Once airleak resolved, the priority again became an arterial oxygen saturation of ≥90%, with an FIO_2 of ≤0.6, and the mean airway pressure was decreased in 1- to 2-cm H_2O increments, as tolerated. When the patient tolerated endotracheal suctioning without significant changes in saturation after reinstitution of high-frequency oscillation and the mean airway pressure was $18 \pm 3 \text{ cm H}_2\text{O}$, a trial of conventional mechanical ventilation was undertaken as previously described for patients with diffuse alveolar disease.

Crossover. Crossover to the alternate ventilator was required if the patient met the following criteria for treatment failure.

- a) Intractable shock with adequate preload and use of maximal inotropic support (Appendix).
- b) Intractable respiratory failure, which was defined as one or both of the following: Pao_2 of <50 torr (<6.7 kPa), with an FIO_2 of 1.0, for at least 2 hrs; pH of <7.20 and Paco_2 of >60 torr (>8.0 kPa) for at least 2 hrs.
- c) An airleak progression of two grades or a worsening grade 4 airleak (Appendix).

If the patient met the criteria for treatment failure after crossover, he/she was excluded from the study and subsequent physiologic data were excluded from analysis.

Study Exit. Exit from the study was mandated if any of the following occurred: a) the patient remained in the study for 30 days or mechanical ventilation/supplemental oxygen was no longer required; b) treatment failure after crossover. Treatment failure was defined as intractable shock, intractable respiratory failure or progression of airleak (see *Crossover* above) (3), a nonpulmonary terminal diagnosis or death (4), or parent- or legal guardian-requested exit from the study.

Data Collection. Physiologic data (heart rate, blood pressure, arterial blood gases) were collected prospectively at 1, 4, 8, 12, 24, 48, and 72 hrs after randomization or after crossover. The frequency and timing of endotracheal tube suctioning, as well as the occurrence rate of endotracheal tube obstruction, were recorded. Chest radiographs were performed 4 hrs after randomization, once at hours 12 and 24 on the day of the study, and then daily for the first week. Subsequently, chest radiographs were performed on study days 9, 11, 13, 15, 22, and 29, or more frequently if clinically indicated. Chest radiographs were

evaluated daily by a radiologist blinded to the mode of ventilation for the presence or absence of hyperinflation as well as for Airleak Score (Appendix). Ventilatory parameters (F_{IO_2} , peak inspiratory pressure, mean airway pressure, end-expiratory pressure, inspiratory time, ventilatory rate, and tidal volume for the conventional ventilation group; and F_{IO_2} , mean airway pressure, pressure amplitude, percent inspiratory time, frequency, and bias flow for the high-frequency oscillation group) were recorded at the same intervals as the physiologic data. All airway pressure measurements were made at the proximal end of the endotracheal tube, using the standard transducers provided with the study ventilators. The oxygenation index was calculated with each arterial blood gas. Airleak Scores were derived daily, based on the chest radiograph and the patient's clinical condition (Appendix). The use of any cardioactive medications or deviations from study protocol were recorded as appropriate.

Data Analysis. The relationship between pairs of dichotomous variables was assessed using a two-tailed Fisher's exact test. Comparisons of continuous measures were performed using a two-tailed Mann-Whitney U test. Repeated-measures analysis of variance, with maximum likelihood estimation for missing data, was used to evaluate the relationships between time and various outcome measures (Pao_2/PAO_2 ratio, $Paco_2$, mean airway pressure, and oxygenation index) in each ventilatory group. Repeated-measures analysis of covariance, with maximum likelihood estimation, was used to evaluate differences between the ventilatory groups over time for the same outcome measures. Polychotomous logistic regression was used to examine the relationship between patterns of ventilatory usage and an ordinal measure of treatment outcome (9). The level of treatment effectiveness was ranked ordinally: a) survival without severe chronic lung disease; b) survival with severe chronic lung disease (requirement for supplemental oxygen at 30 days); and c) death. Four pretreatment conditions (institution, patient weight, initial Airleak Score, and the initial Pao_2/PAO_2 ratio) were initially evaluated based on the improvement in chi-square statistic in the polychotomous regression. As none of the pretreatment conditions was significantly related to the ordinal outcomes, they were excluded from subsequent analyses. The specific ventilatory usage pattern was then evaluated, using the improvement in chi-square statistic in the polychotomous regression. In all cases, a $p < .05$ was considered statistically significant.

RESULTS

Patient Description. Seventy patients were enrolled and randomized between July 1990 and January 1994.

The analysis did not include the data from six patients because these patients had been excluded from the study within 8 hrs of enrollment. Four patients were excluded due to protocol violations (three of these patients were crossed-over inappropriately and one patient failed to cross over after meeting the study entry criteria). Two patients were transferred to another institution before completing the protocol and were also excluded from the analysis. Fifty-eight patients were included in the data analysis (29 patients in the conventional ventilation group and 29 patients in the high-frequency oscillation group) (Fig. 1).

Patient diagnoses included adult respiratory distress syndrome ($n = 32$; 55%), viral pneumonia ($n = 20$; 34%), bacterial pneumonia ($n = 5$; 9%), and pulmonary hypoplasia ($n = 1$). The distribution of diagnoses was not significantly different between ventilatory groups. All patients except two patients in the conventional ventilation group and one patient in the high-frequency group received muscle relaxants at the time of enrollment. Both ventilatory groups were comparable for age, weight, sex, duration of mechanical ventilation before enrollment, severity of illness, initial ventilatory settings, enrollment category, and initial Airleak Score (Table 1). Endotracheal tube suctioning was performed between a mean of three and five times per day during the first 72 hrs of study and there were no significant differences between the ventilatory groups or significant associations with time.

Gas Exchange Parameters. There was a significant ($p < .001$) association between time and an increasing Pao_2/PAO_2 ratio in the high-frequency oscillation group, which was not evident in the patients managed with

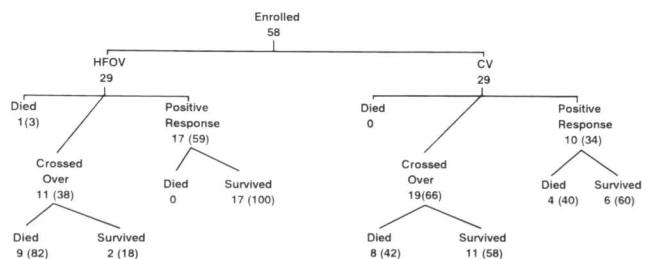


Figure 1. Patient flow after enrollment in the study. Only patients included in subsequent data analysis are depicted. Data are presented as number of patients, with percentage of previous subgroup in parentheses. A positive ventilatory response is defined as the absence of treatment failure criteria before either study exit or death. The condition of one patient, who was randomized to receive high-frequency oscillatory ventilation, acutely deteriorated after 5 days in the study, and this patient never fulfilled the criteria for crossover. Four patients in the conventional ventilatory group demonstrated a positive response but were excluded from the study before crossover, due to the development of a nonpulmonary terminal diagnosis. *HFOV*, high-frequency oscillatory ventilation; *CV*, conventional ventilation.

Table 1. Patient demographics

	CV	HFOV
No. of patients	29	29
Age (yr)	2.5 ± 2.5	3.1 ± 3.3
Weight (kg)	13.1 ± 7.6	13.6 ± 9.4
Male/female ratio	2.2	1.9
Duration of MV before enrollment (hr)	80 ± 81	143 ± 240
PRISM score	11 ± 5	11 ± 5
OI at enrollment	28.5 ± 14.2	25.5 ± 9.6
Paw at enrollment (cm H ₂ O)	21.3 ± 4.8	21.5 ± 3.4
PIP at enrollment (cm H ₂ O)	42 ± 11	42 ± 8
PEEP at enrollment (cm H ₂ O)	10 ± 2	11 ± 2
FiO ₂ at enrollment	0.83 ± 0.18	0.84 ± 0.15
Pao ₂ /PaO ₂ ratio at enrollment	0.13 ± 0.05	0.13 ± 0.04
Enrollment Category		
DAD	26 (90)	24 (83)
ALS	3 (10)	5 (17)
No. requiring vasopressors (%)	18 (62)	17 (59)
No. with oncologic diagnosis (%)	2 (7)	3 (10)
AL Score at entry	0.8 ± 1.1	0.9 ± 1.2

CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; MV, mechanical ventilation; PRISM, Pediatric Risk of Mortality; OI, oxygenation index; Paw, mean airway pressure; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; DAD, diffuse alveolar disease; ALS, airleak syndrome; AL, airleak.

Data are mean ± SD, except enrollment category, number requiring vasopressors, and number with oncologic diagnosis, which are presented as number (%), and male/female ratio. There were no significant differences between ventilator groups.

conventional ventilation. There were no significant differences in Paco₂ between the groups or a significant association between Paco₂ and time in either group (Fig. 2). The mean airway pressure was significantly ($p < .001$) higher in the high-frequency oscillation group during the first 72 hrs of study. There was a significant ($p = .001$) relationship between time and a decreasing oxygenation index in the high-frequency oscillation group but not in the conventional ventilation group (Fig. 3).

Outcome Data. There were no differences between the groups in duration of mechanical ventilation, frequency of airleak, Airleak Scores, frequency of crossover, or 30-day survival (Table 2). Significantly fewer patients treated with high-frequency oscillatory ventilation required supplemental oxygen at 30 days compared with patients managed with conventional ventilation ($p = .039$; odds ratio 5.4; 95% confidence interval 1.2 to 23.2). There were no unanticipated neurologic events during high-frequency oscillatory ventilation and there was no significant difference in

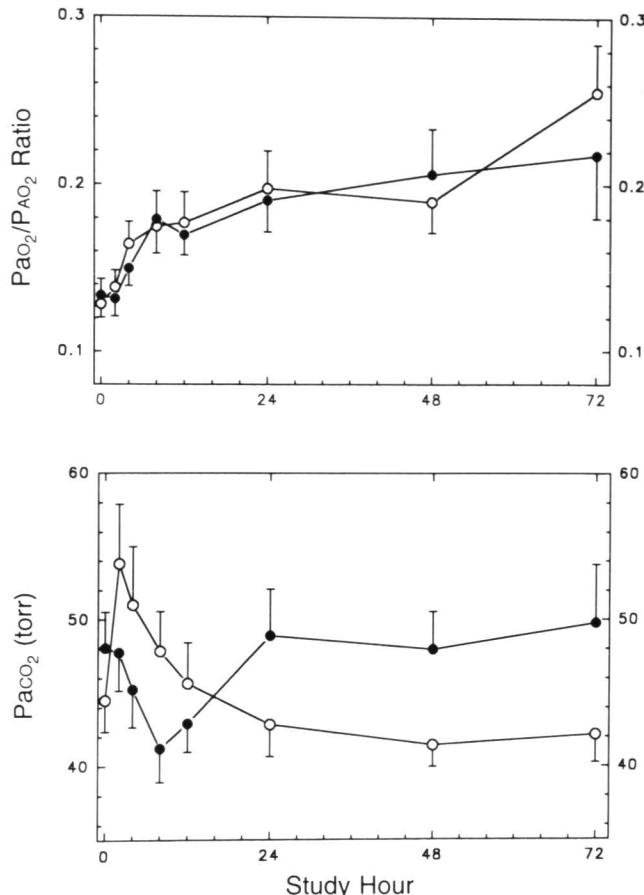


Figure 2. Pao₂/PaO₂ ratio and Paco₂ during the first 72 hrs of study for both high-frequency oscillatory ventilation (open circles) and conventional ventilation (closed circles) groups. Time 0 represents the last ventilator and physiologic parameters before enrollment. Data are mean ± SEM. There was a significant ($p < .001$) association between an increasing Pao₂/PaO₂ ratio and time in the high-frequency oscillation group that was not seen in the patients managed with conventional ventilation. There were no significant differences in Paco₂ between the two ventilatory groups. At 72 hrs, there were 22 patients in the high-frequency oscillatory ventilation group and 16 patients in the conventional ventilation group.

the frequency of neurologic complications between ventilatory groups.

Ranked outcome analysis demonstrated a significant relationship between overall ventilatory usage pattern and ranked outcomes (Table 3). When ventilatory subgroups were compared, the patients managed with high-frequency oscillatory ventilation only (i.e., patients not crossed over to conventional ventilation from high-frequency ventilation or to high-frequency ventilation from conventional ventilation) had significantly ($p = .003$) better ranked outcomes than patients managed with conventional ventilation only. The patients who crossed over from conventional to high-frequency ventilation had significantly ($p = .02$)

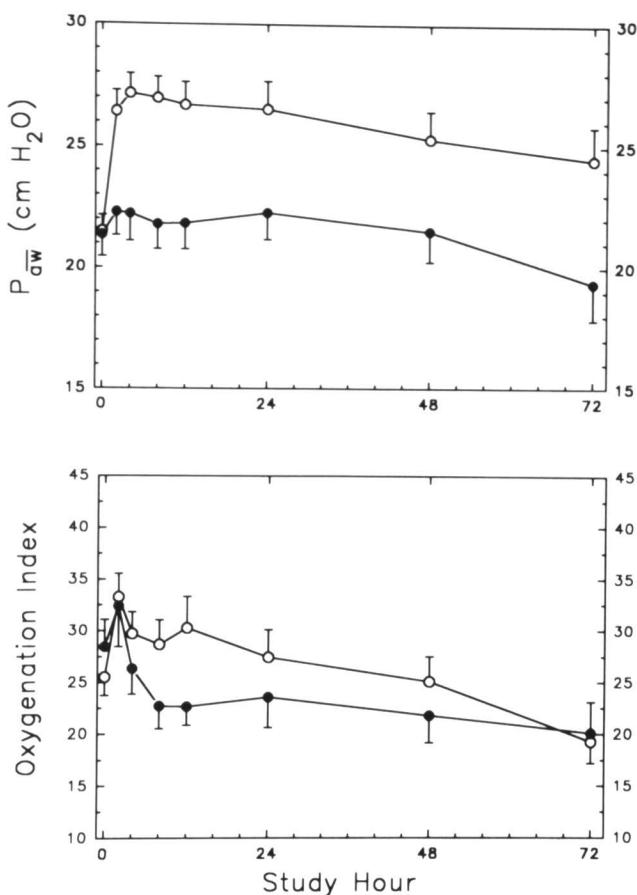


Figure 3. Mean airway pressure (Paw) and oxygenation index during the first 72 hrs of study for both high-frequency oscillatory ventilation (open circles) and conventional ventilation (closed circles) groups. Time 0 represents the last ventilatory and physiologic parameters before enrollment. Data are mean \pm SEM. The Paw in the high-frequency oscillatory ventilation group was significantly ($p < .001$) higher than in the conventional ventilation group. There was a significant ($p = .001$) association between a decreasing oxygenation index and time in the high-frequency oscillation group that was not seen in the group managed with conventional ventilation. At 72 hrs, there were 22 patients in the high-frequency oscillatory ventilation group and 16 patients in the conventional ventilation group.

better ranked outcomes than patients who crossed over from high-frequency to conventional ventilation. Finally, the patients who finished the study using high-frequency oscillatory ventilation had significantly ($p = .001$) better ranked outcomes than those patients who finished the study using conventional ventilation.

Analysis of Crossover Patients. After crossover, significantly ($p = .008$) more patients crossed over to high-frequency oscillatory ventilation and demonstrated a higher ($\geq 20\%$ increase) Pao_2/PAO_2 ratio at 8 hrs (Table 4). There was a significant ($p = .003$) association between time and an increasing Pao_2/PAO_2 ratio in the patients who crossed over to high-frequency oscillatory ventilation. This significant

Table 2. Comparison of outcomes (by initial assignment)

	CV	HFOV
No. of patients	29	29
Total ventilator days	22 ± 17	20 ± 27
Total ventilator days (survivors at 30 days)	29 (18)	27 (31)
Total ventilator days (nonsurvivors at 30 days)	11 (9)	8 (6)
No. of patients who developed ALS on protocol (%)	6 (32)	4 (25)
Highest Airleak Score	1.9 ± 1.8	1.4 ± 1.5
No. with Airleak Score of 3 or 4 (%)	13 (45)	9 (31)
Total no. of crossovers (%)	19 (66)	11 (38)
No. of crossovers due to hypoxemia (%)	7 (37)	2 (18)
No. of crossovers due to hypercarbia (%)	2 (11)	3 (27)
No. of crossovers due to intractable shock (%)	1 (5)	3 (27)
No. of crossovers due to airleak (% of crossovers)	9 (47)	3 (27)
Duration of MV before crossover (hr)	67 ± 84	74 ± 75
No. requiring supplemental oxygen at 30 days (% of survivors)	10 (59) ^a	4 (21) ^a
No. of survivors at 30 days (%)	17 (59)	19 (66)
Neurologic events on study (% of patients)	2 (7)	1 (3)

CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; ALS, airleak syndrome; MV, mechanical ventilation.

Data are mean \pm SD, except where otherwise indicated.

^a $p = .039$.

Table 3. Ranked outcomes vs. pattern of ventilator usage

	HFOV	CV to HFOV	CV	HFOV to CV
Survival without severe lung disease (%)	83	21	30	0
Survival with severe lung disease (%)	11	37	30	18
Death (%)	6	42	40	82

HFOV, high-frequency oscillatory ventilation; CV, conventional ventilation.

Severe lung disease was defined as the requirement for supplemental oxygen with an FIO_2 of > 0.3 at 30 days. The overall relationship between ranked outcome and pattern of ventilator usage was highly significant ($p < .001$).

association was not seen in the patients who crossed over to conventional ventilation (Fig. 4). There was also a significant association between time and a decreasing oxygenation index in both crossover groups ($p = .03$ for patients crossed over to conventional ventilation and $p = .02$ for patients crossed over to high-frequency oscillation) during the first 72 hrs after crossover. However, there was no significant

Table 4. Analysis of crossover patients

	CV to HFOV	HFOV to CV
No. (% total group) ^a	19 (66)	11 (38)
Improvement in oxygenation ($\geq 20\%$ increase in $\text{Pao}_2/\text{PAO}_2$ ratio at 8 hrs)	12 (75) ^b	1 (8) ^b
Improvement in ventilation ($\geq 20\%$ decrease in PCO_2 at 8 hrs)	6 (50)	4 (44)
No. successful (% of crossovers)	15 (83)	7 (78)
Overall survival (at 30 days)	11 (58)	2 (18)

CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation.

Data are presented as number (%).

^aComplete postcrossover data are not available for three patients and are excluded from the remainder of the table (except overall survival); ^b $p = .008$.

difference in postcrossover oxygenation index between the groups.

Predictors of Survival in Patients Treated With High-Frequency Oscillatory Ventilation. Given the success of high-frequency oscillation in improving outcome, we sought to develop time-sensitive predictors of the survival rate in patients managed with high-frequency oscillation. The group comprised 48 patients: 29 primary high-frequency oscillatory ventilation patients and 19 patients who failed controlled ventilation and were crossed over to high-frequency oscillatory ventilation. Thirty (63%) of these patients survived and 18 died. We then evaluated the significance of 11 pretreatment conditions (age, duration of pretreatment ventilation, frequency of an oncologic diagnosis, oxygenation index, mean airway pressure, peak inspiratory pressure, end-expiratory pressure, FiO_2 , $\text{Pao}_2/\text{PAO}_2$ ratio, frequency of airleak, or Airleak Score), measured either before randomization or crossover, in identifying those patients who survived. The only pretreatment variable that was significantly different in the survivors was age. The mean age of survivors treated with high-frequency oscillation was 1.9 yrs compared with 4.5 yrs in nonsurvivors ($p = .002$). We then evaluated the significance of two post-treatment variables (oxygenation index and $\text{Pao}_2/\text{PAO}_2$ ratio) during the first 72 hrs of high-frequency oscillation in identifying survivors. The oxygenation index in survivors was significantly ($p < .001$) lower compared with nonsurvivors during the first 72 hrs of therapy. Furthermore, there was a significant association between time and a decreasing oxygenation index in survivors ($p < .001$), as well as time and an increasing

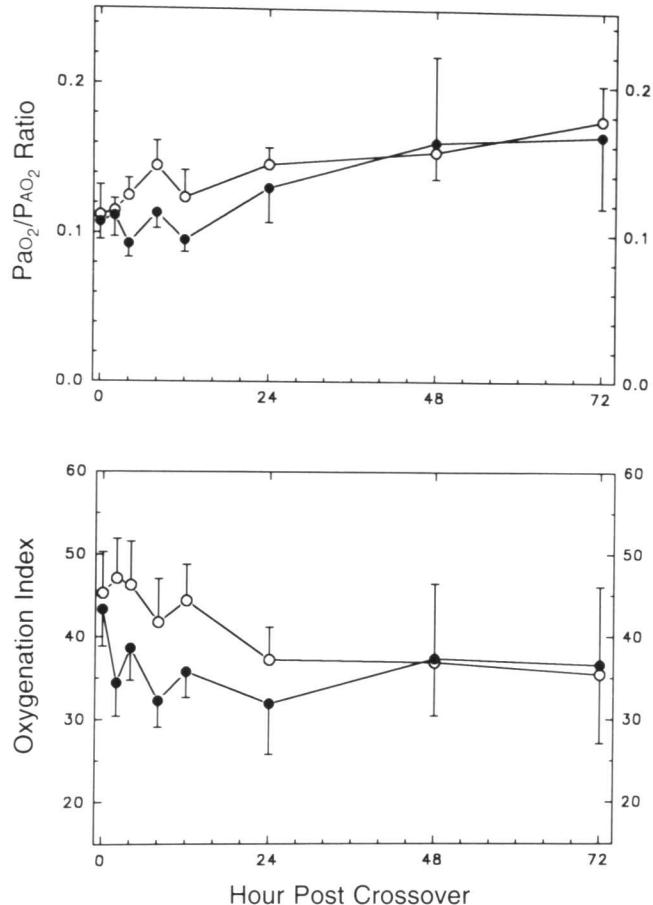


Figure 4. $\text{Pao}_2/\text{PAO}_2$ ratio and oxygenation index during the first 72 hrs after crossover to the alternate ventilator. Patients who were crossed over from conventional ventilation to high-frequency oscillatory ventilation are represented by open circles and patients who were crossed over from high-frequency oscillatory ventilation to conventional ventilation are represented by closed circles. Data are mean \pm SEM. There was a significant ($p = .003$) association between time and an increasing $\text{Pao}_2/\text{PAO}_2$ ratio in the group that was crossed over from conventional ventilation to high-frequency oscillatory ventilation that was not seen in the group that was crossed over from high-frequency oscillation to conventional ventilation. There was also a significant association between time and a decreasing oxygenation index in both crossover groups ($p = .03$ for patients who were crossed over to conventional ventilation; $p = .02$ for patients who were crossed over to high-frequency oscillatory ventilation). At 72 hrs, there were 11 patients remaining in the group who were crossed over to high-frequency oscillatory ventilation (open circles) and there were 4 patients in the group who were crossed over to conventional ventilation (closed circles).

oxygenation index in the nonsurvivors ($p = .03$) (Fig. 5). There was also a significant ($p = .004$) difference between $\text{Pao}_2/\text{PAO}_2$ ratio during the first 72 hrs of high-frequency oscillation in the survivors and nonsurvivors; furthermore, there was a significant association between time and an increasing $\text{Pao}_2/\text{PAO}_2$ ratio during the first 72 hrs, which was not seen in the nonsurvivors.

We then performed a stepwise, multiple logistic regression to further evaluate the variables most significantly associated with survival. Pretreatment age ($p = .004$) and oxygenation index at 24 hrs ($p = .006$) were the two variables that predicted survival independently. Age was a less powerful predictor of survival than oxygenation index when examined in 2×2 contingency tables (odds ratio 6.5 vs. 20.8). An oxygenation index of ≥ 42 at 24 hrs predicted the mortality rate with an odds ratio of 20.8 (95% confidence interval 3.4 to 128.6; $p < .001$), a sensitivity of 62%, and a specificity of 93% (Fig. 6).

DISCUSSION

This is the first randomized study comparing high-frequency oscillation with conventional mechanical ventilation in the pediatric population. Our results indicate that high-frequency oscillatory ventilation, utilizing an aggressive volume recruitment strategy, results in significant improvement in oxygenation compared with a conventional ventilatory strategy that is designed to limit increases in peak airway pressures. Furthermore, despite the use of higher mean airway pressures, the optimal lung volume strategy used in this study was associated with a lower frequency of barotrauma, as indicated by requirement for supplemental oxygen at 30 days, and improved outcome compared with conventional mechanical ventilation.

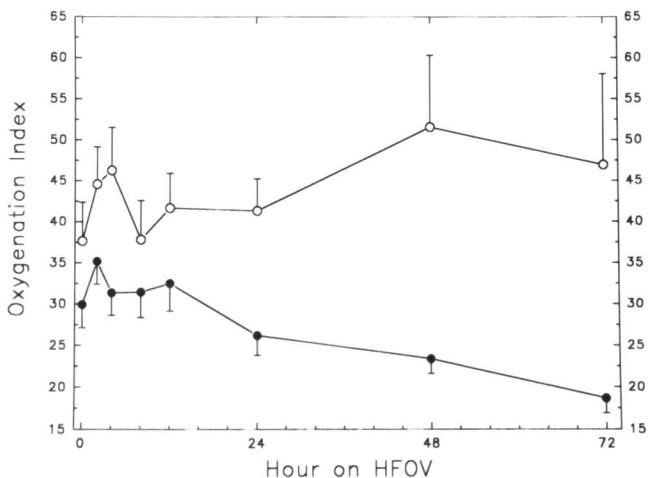


Figure 5. The oxygenation index was significantly ($p < .001$) lower in survivors (closed circles) compared with nonsurvivors (open circles) during the first 72 hrs of therapy. Furthermore, there was a significant association between time and a decreasing oxygenation index in survivors ($p < .001$), as well as time and an increasing oxygenation index in the nonsurvivors ($p = .03$) (Fig. 4). The mean oxygenation index of the survivors at 24 hrs after institution of high-frequency oscillatory ventilation (HFOV) was 26.2, which was significantly ($p = .004$) lower than the mean oxygenation index of nonsurvivors (41.4). Data are mean \pm SEM.

The aggressive strategy utilized in our study, which attempted to rapidly achieve and maintain the "ideal" lung volume, has been convincingly shown in animals to result in significant improvement in oxygenation and pulmonary mechanics and is also associated with decreased histologic evidence of barotrauma (10–12). Recent trials (1, 2) in premature infants with hyaline membrane disease utilizing this approach have also shown a decreased frequency of clinically-evident barotrauma. This strategy, although associated with significant increases in proximal mean airway pressure, produces very small phasic changes in alveolar pressure and volume (13), and these small phasic changes may be critical in preventing further lung injury (14). Our data suggest that the recruitment of optimal lung volume and the limitation of alveolar pressure change during the respiratory cycle do reduce pulmonary morbidity and mortality rates in pediatric patients. We acknowledge that the mode of ventilation was not completely blinded and subtle biases favoring one mode of ventilation may have been introduced. However, the majority of the data we collected were quantitative physiologic and ventilatory variables.

Only eight patients with severe airleak were included at study entry. Consequently, it is difficult to speculate about the utility of an aggressive volume recruitment strategy in the management of airleak. However, a recent study (2) of premature infants at high risk for the development of airleak demonstrated a decreased frequency of airleak syndromes in infants managed with a high-frequency oscillatory ventilation strategy similar to the one we have described.

Previous experience (6) in pediatric patients with acute hypoxic respiratory failure indicates that the oscillator strategy used in this study, despite significant

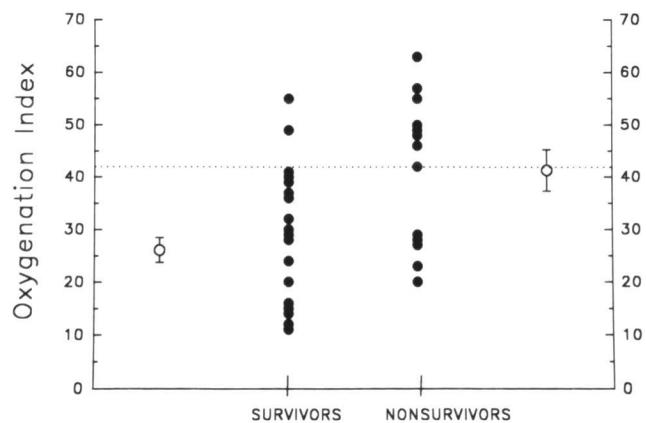


Figure 6. Oxygenation index at 24 hrs in survivors and nonsurvivors (mean \pm SEM). An oxygenation index of ≥ 42 at 24 hrs predicted mortality, with an odds ratio of 20.8 (95% confidence interval 3.4 to 128.6; $p < .001$), a sensitivity of 62%, and a specificity of 93%.

increases in mean airway pressure, does not produce hemodynamic compromise and, therefore, global oxygen delivery is preserved. Despite theoretical concerns regarding compromise of cerebral blood flow during high-frequency oscillation (15), in the present study, there was no evidence of clinically important neurologic injury attributable to the mode of ventilation in the high-frequency oscillatory ventilation group.

We also sought to define predictors of a favorable response to high-frequency oscillatory ventilation in order to allow early identification of patients with high predicted mortality. An oxygenation index of ≥ 42 at 24 hrs identifies a population of patients who may benefit from alternative modes of respiratory support, such as extracorporeal membrane oxygenation (16) or liquid ventilation (17). There is compelling animal evidence that high-frequency oscillatory ventilation may be more effective when used early in the course of respiratory failure in both premature baboons (18, 19) and adult surfactant-depleted rabbits (11). As is evident in our data, a significant number of patients (38% in the present series) do not respond to high-frequency oscillatory ventilation. Furthermore, after crossover to conventional ventilation, these patients have a high mortality rate (82%). The ideal ventilatory approach in pediatric patients with hypoxic respiratory failure may be early institution of an "open lung" strategy, using high-frequency oscillation with rapid identification of patients who are not likely to survive in order to allow institution of other modes of gas exchange before the onset of irreversible lung injury.

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