Original Articles

Controlled Prospective Randomized Comparison of High-Frequency Jet Ventilation and Conventional Ventilation in Neonates with Respiratory Failure and Persistent Pulmonary Hypertension

W. A. Engle, MD
M. C. Yoder, MD
S. P. Andreoli, MD
R. K. Darragh, MD
C. D. Langefeld, MS
S. L. Hui, PhD

OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of high-frequency jet ventilation in near-term and term neonates with persistent pulmonary hypertension.

STUDY DESIGN: Subjects for this prospective, randomized, controlled comparison study were recruited from neonates treated in a level-three neonatal intensive care unit that accepts referrals for extracorporeal membrane oxygenation.

RESULTS: In patients treated with high-frequency jet ventilation ($n = 11$) acute improvement in oxygenation ($p = 0.008$), ventilation ($p < 0.001$), and oxygen indices ($p \leq 0.01$) was demonstrated while stable peak and mean airway pressures were maintained. Control group patients receiving high-frequency positive pressure ventilation with a conventional ventilator required increasingly higher peak inspiratory pressures ($p = 0.005$) to maintain oxygenation, ventilation, and oxygen indices. There were no significant differences in survival without use of extracorporeal membrane oxygenation, nor were there differences in duration of oxygen therapy, ventilation, and hospitalization; need for extacorporeal membrane oxygenation; or incidence of chronic lung disease.

CONCLUSIONS: High-frequency jet ventilation acutely improves oxygenation and ventilation without significantly increasing morbidity. Therefore high-frequency jet ventilation may be a useful adjunct for stabilization of the conditions of neonates with severe persistent pulmonary hypertension. Conclusions about the efficacy of high-frequency jet ventilation in improving survival without the need for extracorporeal membrane oxygenation await multicentered, collaborative investigations with large cohorts of patients. *(J Perinatol 1997;17:3-9.)*

Departments of Pediatrics and Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Address correspondence and reprint requests to W. A. Engle, MD, Riley Hospital for Children, 702 Barnhill Dr., RR208, Indianapolis, IN 46202-5210.

0743-8346/97 $5.00 + 0 38/1/72315

High-frequency ventilation has been introduced into the treatment of near-term and term neonates with respiratory failure complicated by persistent pulmonary hypertension as a rescue technique when conventional mechanical ventilation appears to be failing.[1-4] These uncontrolled rescue studies suggest that both high-frequency oscillation and high-frequency jet ventilation improve gas exchange and may reduce the need for extracorporeal membrane oxygenation (ECMO).[2,3,5] Carter et al.[2] suggest that high-frequency oscillation decreases the need for ECMO by 46%. Spitzer et al.[3] and Gonzales et al.,[5] reporting on separate experiences, suggest that the use of extracorporeal circulation may be reduced 39% and 51%, respectively, with high-frequency jet ventilation. Other investigators studying the efficacy of high-frequency jet ventilation in near-term and term neonates with respiratory failure, however, were not able to confirm improved survival.[1]

None of the studies that reported experiences with high-frequency jet ventilation in the term neonate have been randomized, controlled trials and are subject to criticisms regarding use of historic controls and treatment bias.[1,3,5] The purpose of this study was to compare the efficacy and safety of high-frequency jet ventilation with conventional ventilation in near-term and term neonates with respiratory failure complicated by persistent pulmonary hypertension. Specifically, we were interested in understanding the acute effects of high-frequency jet ventilation on oxygenation, ventilation, and level of mechanical ventilation. We were also interested in knowing whether a clear advantage with respect to survival without ECMO, incidence of chronic lung disease, duration of mechanical ventilation and hospitalization, and need for ECMO was conferred with the use of high-frequency jet ventilation.

METHODS

Our study was a prospective, randomized, controlled comparison of high-frequency jet ventilation and conventional ventilation in the treatment of near-term and term neonates with respiratory failure and pulmonary hypertension. Patient enrollment occurred from April 1990 through June 1992. The study was approved by the institutional review board of the hospital. Patients eligible for this study included neonates with birth weights >2000 gm and gestational ages ≥35 weeks who were receiving mechanical ventilation and a fraction of inspired oxygen (Fio_2) of 1.0. Furthermore, eligible patients were required to have a clinical diagnosis of persistent pulmonary hypertension of the newborn, meconium aspiration or other aspiration syndrome, sepsis or pneumonia, transient tachypnea of the newborn, or respiratory distress syndrome. Patients with congenital heart disease or lethal congenital anomalies were excluded from study entry. All of the study patients received a trial of high-frequency positive pressure ventilation to achieve respiratory alkalosis (arterial carbon dioxide tension [$Paco_2$] <30 torr) with use of the conventional ventilator before study enrollment. Arterial blood gas goals and specifics of patient treatment were determined by one of the eight attending neonatologists. A predicted mortality rate of 60%, as defined by an oxygenation index ≥25 for 2 hours or an alveolar-arterial oxygen gradient ($A\text{-}aDo_2$) ≥600 for 4 hours, was also required for inclusion in the study.[6] Oxygenation index (OI) and $A\text{-}aDo_2$ were calculated according to the following formulas:

$$OI = \frac{(\text{Mean airway pressure})\,(Fio_2)\,(100)}{Pao_2}$$

$$A\text{-}aDo_2 = (713)(Fio_2) - Pao_2 - \frac{Paco_2}{0.8}$$

where Pao_2 is arterial oxygen tension. Persistent pulmonary hypertension was defined by echocardiography.

Patients were randomly assigned by a table of random numbers to either the conventional ventilator or the high-frequency jet ventilator treatment after eligibility criteria were met and informed consent obtained.

In patients randomized to receive high-frequency jet ventilation, ventilation strategy was conducted according to guidelines of Spitzer et al.[8] This process included reintubation with a triple-lumen endotracheal tube (Hi-Lo tube; Mallinckrodt Medical, Inc., St. Louis, Mo.). High-frequency jet ventilation (Bunnell Life Pulse; Bunnell, Inc., Salt Lake City, Utah) was initiated at a peak inspiratory pressure similar to that of conventional ventilation and weaned rapidly in the presence of excessive patient vibration and then weaned gradually according to blood gas values and clinical condition. Initial high-frequency jet ventilator rate was 420 breaths/min and the inspiratory time on the jet valve was 0.02 seconds. Fio_2 was decreased gradually. The peak inspiratory pressure on the conventional ventilator (model IV 100B; Sechrist Industries Inc., Anaheim, Calif.) was set 2 to 6 cm H_2O lower than that on the high-frequency jet ventilator to prevent interruption of the high-frequency breaths. Conventional ventilator rate was decreased according to oxygenation status to 5 to 15 breaths/min with an upper limit of 20 breaths/min during initiation of high-frequency jet ventilation. The peak inspiratory pressures on both high-frequency jet and conventional ventilators and Fio_2 were decreased according to blood gas values (Pao_2 < 30 torr [4.01 kPa]) and clinical stability until the peak inspiratory pressure was 18 to 24 cm H_2O and the Fio_2 was <0.6. At this point, conventional ventilation alone was continued at the discretion of the attending neonatologist.

In patients randomized to receive conventional ventilation, the ventilation strategy included a trial of more vigorous high-frequency positive pressure ventilation (hyperventilation) to induce hypocarbia ($Paco_2$ <25 torr [3.3 kPa]) or respiratory alkalosis (pH >7.50), or both.

If the patient's condition deteriorated despite maximum conventional ventilation or high-frequency jet ventilation and fulfilled institutional criteria predictive of an 80% or greater mortality rate (for example, oxygenation index >40 for 2 hours, >35 for 6 hours,[7] treatment with ECMO was recommended to the parents. Failure of the randomized mode of ventilator was defined as the need for ECMO or death. Crossover between high-frequency jet ventilation and conventional ventilation for patients in whom the randomized mode of ventilation failed was not allowed because of the critical instability of the clinical condition of these patients just before ECMO.

Data gathered included demographic information, arterial blood gas values beginning 1 hour before study entry through the time that the clinical condition improved or the randomized ventilator therapy failed, survival, randomization status, age at randomization, medications administered before study entry, duration of both conventional and high-frequency ventilation, and echocardiographic evidence of pulmonary hypertension. Other data collected included the average oxygenation index and $A\text{-}aDo_2$ for 4 hours preceding randomization, ventilator parameters, Fio_2, and timing and need for ECMO. Measures of morbidity included duration of oxygen administration, presence of abnormal findings on chest radiograph and oxygen supplementation for ≥30 days (chronic lung disease), resumption of conventional ventilation because of mechanical malfunction of the high-frequency jet ventilator or acute deterioration of the patient's condition while receiving high-frequency jet

Table 1 — Patient Demographics

	HFJV ($n = 11$)	Control ($n = 13$)	Significance
Birth weight (gm)	3222 ± 553	3183 ± 562	$p = 0.79$
Gestational age (wk)	39.3 ± 2.9	38.9 ± 2.2	$p = 0.85$
Age at study entry (hr)	24.6 ± 9.8	22.0 ± 18.2	$p = 0.19$
Entry criteria			
No. of patients with OI ≥25 for 2 hours	9 (82%)	11 (85%)	$p = 1.00$
No. of patients with A-aDo_2 ≥600 for 4 hours	10 (91%)	6 (46%)	$p = 0.02$
Degree of illness			
Mean OI for 4 hours before study entry	33.1 ± 12.1	33.1 ± 9.0	$p = 0.90$
Mean A-aDo_2 for 4 hours before study entry	623.1 ± 12.7	609.5 ± 19.7	$p = 0.13$
Primary diagnoses (No.)			
Meconium aspiration	4	3	
Persistent pulmonary hypertension	3	2	
Sepsis/pneumonia	4	2	
Transient tachypnea	0	1	
Immune hydrops	0	2	
Hyaline membrane disease	0	2	
Echocardiographic evidence for pulmonary hypertension (No.)*	11	13	$p = 1.00$
Surfactant administration before study entry (No.)	1	4	$p = 0.34$

Values given as mean plus or minus standard deviation where appropriate. *HFJV*, High-frequency jet ventilation; *OI*, oxygenation index.
*Echocardiographic evidence of pulmonary hypertension could include right-to-left shunt through foramen ovale or ductus arteriosus, tricuspid regurgitent flow greater than 3 cm/sec, or bowing of interatrial septum into left atrium as interpreted by pediatric echocardiographer.

ventilation, evidence of tracheitis or tracheal mucosa slough or obstruction, pneumothorax, other air leak phenomena, head ultrasonographic or computed tomographic evidence of intracranial hemorrhage, hydrocephalus or periventricular leukomalacia, seizures, sepsis, meningitis, pneumonia, other complications, age at hospital discharge, and age and cause of death.

The study was closed after 2 years of enrollment because of lack of dramatic survival advantage with high-frequency jet ventilation, demonstrated physiologic advantage, and initiation of a trial of inhaled nitric oxide. Analysis of the data demonstrated physiologic advantage to high-frequency jet ventilation; a survival outcome advantage was not present. The *t* test, Wilcoxon ranked sums tests, chi square tests, or Ficher's exact tests were used to investigate the differences between high-frequency jet ventilation and conventional ventilation groups. A survival analysis was computed to test whether overall time until need for ECMO or death was different between the two ventilation techniques.[9] Finally, a single-factor repeated-measures analysis of variance was used to assess whether there were significant changes in the ventilation parameters from 1 hour before study entry to 6 hours after entry. All tests of statistical significance were based on a two-sided hypothesis; $p < 0.05$ was considered significant.

RESULTS

Thirteen patients were randomized to the control group and 11 to the high-frequency ventilator group. The study groups were similar in birth weight, gestational age, age at study entry, and severity of illness before entry into the study (Table 1). The number of patients with A-aDo_2 values >600 for 4 hours was significantly greater in the high-frequency jet ventilator group. This difference reflects that a larger number of patients in the high-frequency jet ventilator group were successfully undergoing hyperventilation at the time of study entry; a lower $Paco_2$ results in a higher A-aDo_2. Primary diagnoses were similar and all of the patients had echocardiographic evidence of pulmonary hypertension. The use of surfactant before study entry was infrequent and did not differ between the study groups and there were no differences between groups in the use of sodium bicarbonate boluses or constant infusions, volume expanders, dopamine, dobutamine, pancuronium bromide, ampicillin, gentamicin, morphine sulfate, or secobarbital (data not shown). Isoproterenol, epinephrine, tolazoline, fentanyl, and diazepam were used infrequently (data not shown).

There were no differences in age at initiation of ECMO or age at death. The conditions of those patients who either died or were treated with ECMO who received high-frequency jet ventilation deteriorated at a median of 49.7 hours (range 6.3 to 92.9 hours) after study entry compared with a median of 8.6 hours (range 5.3 to 162.1 hours) in patients receiving conventional ventilation. Treatment failure occurred in only two patients in the high-frequency jet ventilation group within 12 hours of study entry whereas seven of the conventionally treated patients either died or were

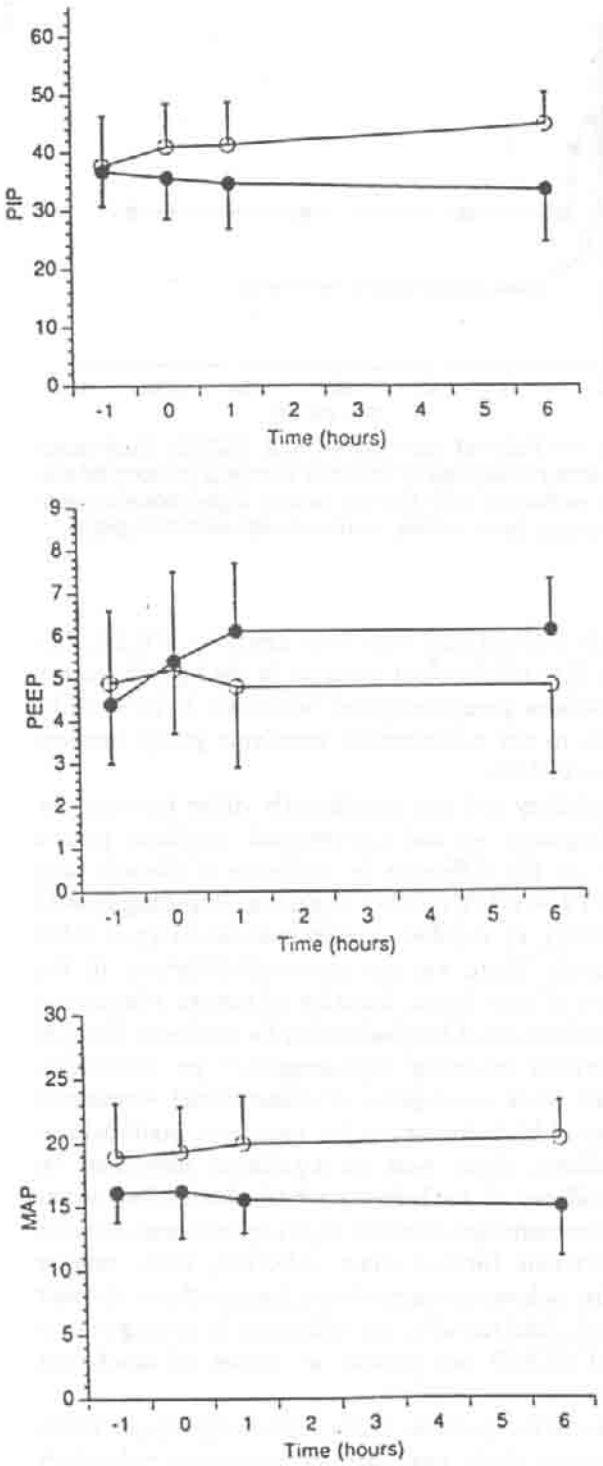

Figure 1 – Peak inspiratory pressure *(PIP)*, positive end-expiratory *(PEEP)*, and mean airway pressure *(MAP)* for 6 hours after study entry. In conventional ventilator group *(open circles)* peak inspiratory pressure increased significantly ($p < 0.01$). In high-frequency jet ventilator group *(closed circles)* positive end-expiratory pressure increased significantly ($p < 0.01$). Other measures of ventilation requirements did not significantly change in study groups. Units for peak inspiratory pressure, positive end-expiratory pressure, and mean airway pressure are centimeters of water.

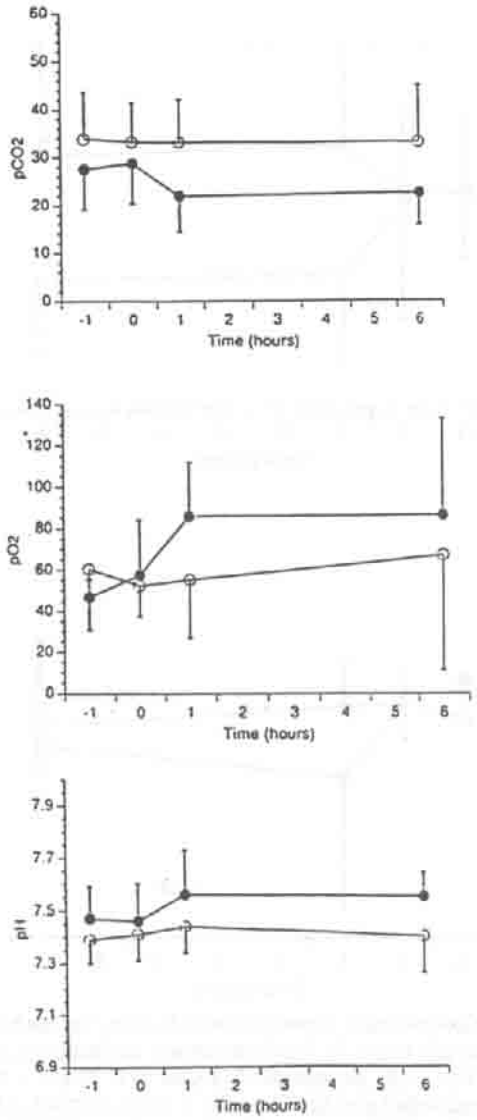

Figure 2 – Values of Po_2, Pco_2, and pH for 6 hours after study entry. in high-frequency ventilator group *(closed circles)*, Pao_2 and pH increased ($p = 0.08$ and $p < 0.001$, respectively) and $Paco_2$ decreased significantly ($p < 0.001$). No significant changes occurred in conventional ventilator group *(open circles)*.

treated with ECMO within 12 hours of study entry ($p = 0.17$).

All patients in both the high-frequency jet ventilation and conventional ventilation groups received an Fio_2 of 1.0 during the first 6 hours after study entry. Figures 1 through 3 depict changes in ventilatory parameters, arterial blood gas values, oxygenation index, and A-aDo_2 from 1 hour preceding study entry through 6 hours after study entry. In the conventionally treated group, only peak inspiratory pressure increased from 37.7 ± 8.6 cm H_2O at study entry to 44.4 ± 5.6 cm H_2O 6 hours after study initiation ($p < 0.01$). There were no other significant changes over time in the con-

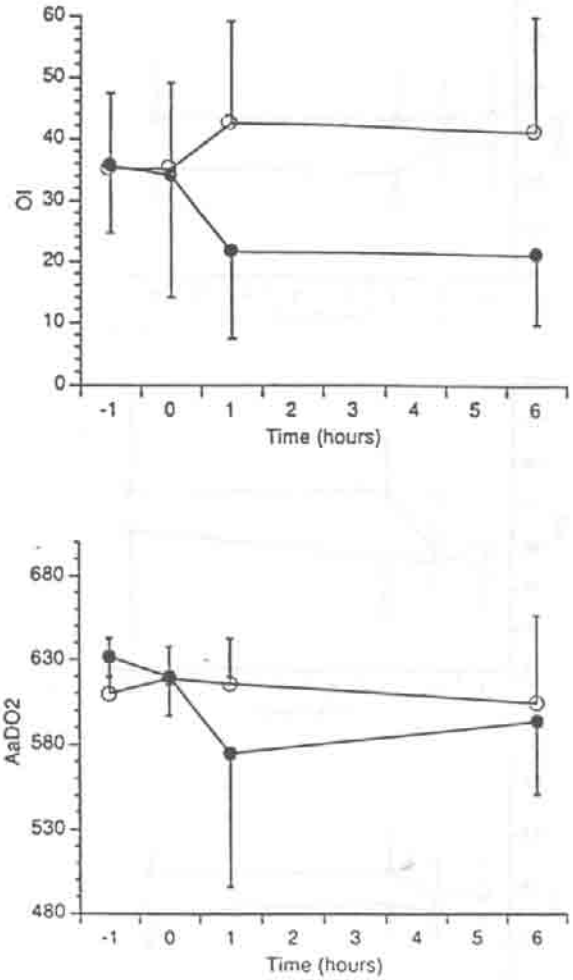

Figure 3 – Oxygenation index *(OI)* and A-aDo_2 values for 6 hours after study entry. In high-frequency ventilator group *(closed circles)*, both oxygenation index and A-aDo_2 decreased significantly ($p < 0.001$ and $p = 0.01$, respectively); neither measure of illness severity changed significantly in conventional ventilator group *(open circles)*.

ventional group. In the patients in the high-frequency jet ventilation group positive end-expiratory pressure increased significantly from 4.4 ± 2.2 torr to 6.1 ± 1.2 torr ($p < 0.01$), whereas peak inspiratory pressure and mean airway pressure did not change (Figure 1). However, a significant increase in Pao_2 (46.9 ± 8.6 torr [6.2 ± 1.1 kPa] versus 86.5 ± 47.0 torr [11.5 ± 6.2 kPa], $p < 0.04$) and pH (7.47 ± 0.12 versus 7.55 ± 0.09, $p < 0.01$) and significant decreases in $Paco_2$ [27.5 ± 8.4 torr [3.7 ± 1.1 kPa] versus 22.3 ± 6.6 torr [3.0 ± 0.9 kPa], $p = 0.01$), oxygenation index (35.9 ± 11.0 versus 20.9 ± 11.4, $p < 0.01$), and A-aDo_2 (631.8 ± 11.7 versus 594.4 ± 43.1, $p = 0.01$) occurred in the high-frequency jet ventilation group of patients.

The high-frequency jet ventilator group did not have a significantly higher rate of survival without ECMO

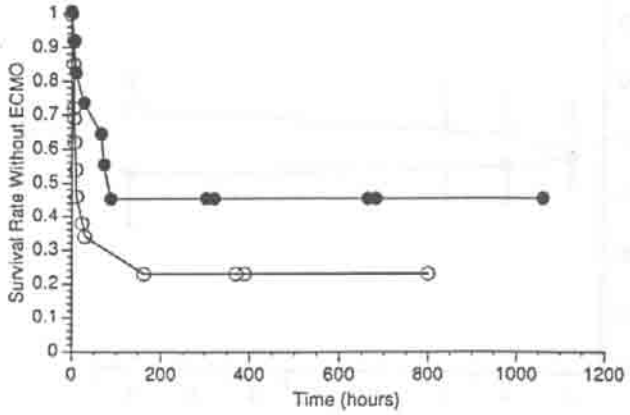

Figure 4 – Rate of survival without ECMO. Each *point* represents percentage of patients surviving to hospital discharge without ECMO. *Closed circles*, high-frequency ventilator group; *open circles*, conventional ventilator group.

than the conventional ventilator group ($p = 0.26$, Figure 4). Five (45%) of 11 patients in the high-frequency jet ventilator group compared with only 3 (23%) of 13 patients in the conventional ventilator group survived without ECMO.

Morbidity did not significantly differ between the high-frequency jet and conventional ventilator groups (Table 2). No difference in incidence of chronic lung disease ($p = 0.10$), number of patients requiring ECMO ($p = 0.11$), or number of pneumothoraces ($p = 0.14$) was noted. There was no statistical difference in the duration of ventilation, duration of oxygen administration, or duration of hospitalization for survivors. None of the patients receiving high-frequency jet ventilation required acute resumption of conventional ventilation because of high-frequency jet ventilator malfunction. In addition, there were no significant differences in the incidence of tracheitis, tracheal obstruction, intracranial hemorrhage, seizures, sepsis, pneumonia, or other complications (urinary tract infection, acute tubular necrosis, pulmonary hemorrhage, hematochezia, or poor feeding). Additionally, no difference in average duration of ECMO per patient or causes of death was evident.

Two of the patients in the high-frequency jet ventilator group died; one died of persistent pulmonary hypertension after consent for ECMO was denied. The other patient in the high-frequency jet ventilator group died of sudden acute myocardial insufficiency as plans for ECMO were being instituted. Of patients in the conventional ventilator group who died, one died of severe hypoxic-ischemic central nervous system insult, another of severe chronic lung disease, and the third of isoimmune hydrops fetalis; all three of these patients who died received ECMO.

Table 2—Morbidity and Mortality Analysis

	HFJV (n = 11)	Control (n = 13)	Significance
Chronic lung disease (No./No. of survivors)	0/9	4/10	$p = 0.08$
Duration of oxygen (days)	16.1 ± 8.2	36.8 ± 48.2	$p = 0.72$
Duration of ventilation (days)	11.8 ± 8.2	24.1 ± 46.2	$p = 0.83$
Duration of HFJV (hr)	89.9 ± 67.8	-	
Duration of hospitalization (days)	25.2 ± 12.7	21.9 ± 17.6	$p = 0.44$
Pneumothorax (No.)	4	1	$p = 0.14$
Tracheitis (No.)	1	0	$p = 0.46$
Tracheal obstruction (No.)	0	1	$p = 1.00$
Intracranial hemorrhage (No.)	0	1	$p = 1.00$
Cerebral infarction (No.)	0	1	$p = 1.00$
Seizures (No.)	2	3	$p = 0.63$
Sepsis (No.)	2	3	$p = 0.63$
Pneumonia (No.)	0	1	$p = 1.00$
ECMO	4	10	$p = 0.11$
Average duration of ECMO (hr)	140.5 ± 90.4	118.4 ± 37.1	$p = 0.51$
Total deaths	2	3	$p = 0.83$
Causes of death			
Hypoxic-ischemic encephalopathy	0	1	
Myocardial insufficiency	1	0	
Chronic lung disease	0	1	
Immune hydrops	0	1	
Persistent pulmonary hypertension of neonate	1	0	

Values given as mean plus or minus standard deviation where appropriate. *HFJV*, High-frequency jet ventilation.

DISCUSSION

The use of high-frequency jet ventilation to treat neonates with respiratory failure complicated by pulmonary hypertension has received attention because of its ability to induce hypocarbia and alkalosis at lower, less traumatic airway pressures.[1,3] We present results from the only randomized, controlled trial comparing the safety and efficacy of high-frequency jet ventilation with conventional ventilation in persistent pulmonary hypertension of the neonate.

We confirmed observations by other investigators that high-frequency jet ventilation improves ventilation (lower $PaCO_2$ values and higher pH) immediately after initiation at peak and mean airway pressures similar to those before high-frequency jet ventilation.[1,3,4,8-11] This was associated with a more pronounced respiratory alkalosis and improved oxygenation. In contrast, to maintain oxygenation and ventilation in the patients receiving conventional ventilator support, peak inspiratory pressure was raised significantly. High-frequency jet ventilation appears to acutely improve oxygenation in severe persistent pulmonary hypertension. This conclusion is supported by our finding that the majority of patients who received high-frequency jet ventilation who either died or required ECMO did so on average 41.1 hours after study entry. These findings suggest that high-frequency jet ventilation may be advantageous in stabilizing oxygenation and ventilation in the critically ill neonate with persistent pulmonary hypertension. Similar findings in a cohort of near-term and term neonates treated with high-frequency jet ventilation have been reported by Baumgart et al.[4] In addition, Baumgart et al.[4] found that a decrease in oxygenation index to <20 within 6 hours of initiation of high-frequency jet ventilation was a sensitive indicator for survival with jet ventilation. Clark et al.[12] reported on a prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for ECMO; they found high-frequency oscillatory ventilation was beneficial in safely stabilizing the conditions of neonates and rescuing them from the need for extracorporeal support or from death.

We did not demonstrate a marked advantage of high-frequency jet ventilation in survival or morbidity because of the small size of our study groups. Multicenter trials with large cohorts of patients will be necessary to definitively determine whether high-frequency jet ventilation reduces mortality and morbidity in neonates with persistent pulmonary hypertension. If the true difference in the survival rates, without resorting to ECMO, is equal to the rates observed in this study (46% versus 23%), we estimate that 66 patients in each group would be required to detect this difference at a 5% level of significance and with 80% power.

An additional problem associated with the small number of patients reported in this study is the inability to assess diagnosis-specific comparisons of high-fre-

quency jet ventilation and conventional ventilation. Baumgart et al.[4] retrospectively found that neonates with severe meconium aspiration syndrome or congenital diaphragmatic hernia were less likely to respond to high-frequency jet ventilation than patients with other causes of pulmonary hypertension. Similar findings have been reported for patients treated with high-frequency oscillatory ventilation.[12] Although all of the patients in this study had persistent pulmonary hypertension, patient diagnoses in the conventional ventilator group were distributed among six diagnostic categories versus three in the high-frequency jet ventilator group. Finally, we did not permit crossover from conventional to high-frequency jet ventilation and vice versa in our study design. We chose this design because of a lower level of complexity for study performance and data analysis. In addition, patients in both ventilator groups were at high risk for mortality and crossover could possibly have delayed institution of life-saving ECMO.

An improved ability to stabilize the conditions of neonates with severe pulmonary hypertension with an unchanged incidence of significant morbidity has been found with the use of high-frequency oscillatory ventilation.[12] Both this study and that comparing high-frequency oscillation with conventional ventilation have been hampered by lower enrollment rates than expected because of the widespread introduction of high-frequency ventilators, use of surfactant, and administration of nitric oxide inhalation by an increasing number of referring hospitals. It is apparent from these studies with small numbers of patients that neither high-frequency jet nor oscillatory ventilation drastically improves survival without need for ECMO. Certain subsets of patients (for example, those with homogeneous lung disease), however, may benefit from either or both of these technologies.[4,12] Therefore future randomized trials of high-frequency ventilation should focus on patients within specific diagnostic categories and include comparison of high-frequency jet ventilation, high-frequency oscillatory ventilation, and conventional ventilation. Use of nitric oxide,[13] surfactant,[14] and conventional ventilation techniques (for example, gentle ventilation[15] or high-frequency positive pressure ventilation[9]) will also need to be controlled.

In summary, we found that high-frequency jet ventilation acutely improves oxygenation, ventilation, and oxygen indices in neonates with persistent pulmonary hypertension. This may prove useful during stabilization of the conditions of severely ill patients. We also demonstrated that high-frequency jet ventilation was not associated with a higher mortality or morbidity than conventional ventilation. A multicenter collaborative trial will be necessary to demonstrate whether high-frequency ventilation reduces mortality and morbidity in neonates with persistent pulmonary hypertension.

Acknowledgment

We would like to thank Lisa Ashman for manuscript preparation and James Lemons, MD, for insightful comments.

References

1. Carlo WA, Boeglos A, Chatburn RL, Walsh MC, Martin RJ. High frequency jet ventilation in neonatal pulmonary hypertension. Arch Pediatr Adolesc Med 1989;143:233-8.
2. Carter JM, Gerstmann DR, Clark RH, et al. High frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990;2:159-64.
3. Spitzer AR, Butler S, Fox WW. Ventilatory response to combined high frequency jet ventilation and conventional mechanical ventilation for the rescue treatment of severe neonatal lung disease. Pediatr Pulmonol 1989;7:244-9.
4. Baumgart S, Hirschl RP, Butler JZ, Coburn CE, Spitzer AR. Diagnosis related criteria in the consideration of extracorporeal membrane oxygenation in neonates previously treated with high frequency jet ventilation. Pediatrics 1992;89:491-4.
5. Gonzales F, Shelton C, Bunnell B, Harris TR. Retrospective review of jet ventilated infants who qualified for extracorporeal membrane oxygenation [Abstract]. Pediatr Pulmonol 1987;3:375.
6. Engle WA, Peters EA, Gunn SK, West KW, Langefeld C, Hui SL. Mortality prediction in near term and term neonates with respiratory failure and interval until death. J Perinatol 1993;13:367-75.
7. Hageman JR, Dusik J, Keuler H. Outcome of persistent pulmonary hypertension of the newborn in relation to severity of presentation. Arch Pediatr Adolesc Med 1988;143:293-6.
8. Spitzer AR, Davis J, Clarke WT, Bernbaum J, Fox WW. Pulmonary hypertension of the newborn. Clin Perinatol 1988;15:389-413.
9. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980.
10. Carlo WA, Chatburn RL, Martin RJ. Decrease in airway pressure during high frequency jet ventilation in infants with respiratory distress syndrome. J Pediatr 1984;104:101-7.
11. Wiswell TE, Foster NH, Slaytor MV, Hachey WE. Management of a piglet model of the meconium aspiration syndrome with high frequency or conventional ventilation. Arch Pediatr Adolesc Med 1992;146:1287-93.
12. Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994;124:447-54.
13. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:819-20.
14. Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full term neonates with severe respiratory failure. Pediatrics 1993;92:135-9.
15. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics 1985;76:488-94.

quency jet ventilation and conventional ventilation. Baumgart et al.[4] retrospectively found that neonates with severe meconium aspiration syndrome or congenital diaphragmatic hernia were less likely to respond to high-frequency jet ventilation than patients with other causes of pulmonary hypertension. Similar findings have been reported for patients treated with high-frequency oscillatory ventilation.[12] Although all of the patients in this study had persistent pulmonary hypertension, patient diagnoses in the conventional ventilator group were distributed among six diagnostic categories versus three in the high-frequency jet ventilator group. Finally, we did not permit crossover from conventional to high-frequency jet ventilation and vice versa in our study design. We chose this design because of a lower level of complexity for study performance and data analysis. In addition, patients in both ventilator groups were at high risk for mortality and crossover could possibly have delayed institution of life-saving ECMO.

An improved ability to stabilize the conditions of neonates with severe pulmonary hypertension with an unchanged incidence of significant morbidity has been found with the use of high-frequency oscillatory ventilation.[12] Both this study and that comparing high-frequency oscillation with conventional ventilation have been hampered by lower enrollment rates than expected because of the widespread introduction of high-frequency ventilators, use of surfactant, and administration of nitric oxide inhalation by an increasing number of referring hospitals. It is apparent from these studies with small numbers of patients that neither high-frequency jet nor oscillatory ventilation drastically improves survival without need for ECMO. Certain subsets of patients (for example, those with homogeneous lung disease), however, may benefit from either or both of these technologies.[4,12] Therefore future randomized trials of high-frequency ventilation should focus on patients within specific diagnostic categories and include comparison of high-frequency jet ventilation, high-frequency oscillatory ventilation, and conventional ventilation. Use of nitric oxide,[13] surfactant,[14] and conventional ventilation techniques (for example, gentle ventilation[15] or high-frequency positive pressure ventilation[9]) will also need to be controlled.

In summary, we found that high-frequency jet ventilation acutely improves oxygenation, ventilation, and oxygen indices in neonates with persistent pulmonary hypertension. This may prove useful during stabilization of the conditions of severely ill patients. We also demonstrated that high-frequency jet ventilation was not associated with a higher mortality or morbidity than conventional ventilation. A multicenter collaborative trial will be necessary to demonstrate whether high-frequency ventilation reduces mortality and morbidity in neonates with persistent pulmonary hypertension.

Acknowledgment

We would like to thank Lisa Ashman for manuscript preparation and James Lemons, MD, for insightful comments.

References

1. Carlo WA, Boeglos A, Chatburn RL, Walsh MC, Martin RJ. High frequency jet ventilation in neonatal pulmonary hypertension. Arch Pediatr Adolesc Med 1989;143:233-8.
2. Carter JM, Gerstmann DR, Clark RH, et al. High frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990;2:159-64.
3. Spitzer AR, Butler S, Fox WW. Ventilatory response to combined high frequency jet ventilation and conventional mechanical ventilation for the rescue treatment of severe neonatal lung disease. Pediatr Pulmonol 1989;7:244-9.
4. Baumgart S, Hirschl RP, Butler JZ, Coburn CE, Spitzer AR. Diagnosis related criteria in the consideration of extracorporeal membrane oxygenation in neonates previously treated with high frequency jet ventilation. Pediatrics 1992;89:491-4.
5. Gonzales F, Shelton C, Bunnell B, Harris TR. Retrospective review of jet ventilated infants who qualified for extracorporeal membrane oxygenation [Abstract]. Pediatr Pulmonol 1987;3:375.
6. Engle WA, Peters EA, Gunn SK, West KW, Langefeld C, Hui SL. Mortality prediction in near term and term neonates with respiratory failure and interval until death. J Perinatol 1993;13:367-75.
7. Hageman JR, Dusik J, Keuler H. Outcome of persistent pulmonary hypertension of the newborn in relation to severity of presentation. Arch Pediatr Adolesc Med 1988;143:293-6.
8. Spitzer AR, Davis J, Clarke WT, Bernbaum J, Fox WW. Pulmonary hypertension of the newborn. Clin Perinatol 1988;15:389-413.
9. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980.
10. Carlo WA, Chatburn RI, Martin RJ. Decrease in airway pressure during high frequency jet ventilation in infants with respiratory distress syndrome. J Pediatr 1984;104:101-7.
11. Wiswell TE, Foster NH, Slaytor MV, Hachey WE. Management of a piglet model of the meconium aspiration syndrome with high frequency or conventional ventilation. Arch Pediatr Adolesc Med 1992;146:1287-93.
12. Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994;124:447-54.
13. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:819-20.
14. Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full term neonates with severe respiratory failure. Pediatrics 1993;92:135-9.
15. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics 1985;76:488-94.