Randomized trial of high-frequency jet ventilation versus conventional ventilation in respiratory distress syndrome

To compare high-frequency jet ventilation (HFJV) with pressure-limited time-cycled conventional ventilation (CV), we randomized 41 infants with clinical and radiographic evidence of respiratory distress syndrome during the first day of life to receive either HFJV or CV. Standardized ventilatory protocols were used for 48 hours, after which CV was administered to both groups. Despite comparable oxygenation (arterial/alveolar oxygen tension ratio), mean airway pressure was lower in the HFJV group (9 ± 2 vs 13 ± 2 cm H_2O, P <0.001), and thus the arterial/alveolar oxygen tension ratio corrected for mean airway pressure was improved in the HFJV group (P <0.05). $Paco_2$ was lower during HFJV (37 ± 3 vs 42 ± 3 mm Hg, P <0.05) despite a comparable peak inspiratory pressure. The incidence of air leaks, progression of intraventricular hemorrhage, and mortality during the 48-hour period did not differ between the two groups. Bronchoscopies in eight infants given HFJV and five given CV revealed no microscopic evidence of necrotizing tracheobronchitis, but one infant given HFJV had evidence of necrotizing tracheitis at autopsy. We conclude that for 48 hours during the acute stage of respiratory distress syndrome, HFJV can maintain adequate gas exchange at lower mean airway pressure than during CV, without an increase in the incidence of side effects. (J PEDIATR 1987;110:275-82)

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The use of assisted ventilation has markedly improved outcome in preterm infants with pulmonary disease. Despite major advances in its application, assisted ventilation occasionally fails to sustain adequate gas exchange in severely ill infants, and respiratory distress syndrome remains the major cause of neonatal mortality.[1] Furthermore, there is high morbidity in infants requiring assisted ventilation; approximately 24% have pulmonary air leaks,[2] and about 20% have bronchopulmonary dysplasia.[3]

$a/A\ O_2$	Arterial/alveolar oxygen tension ratio
CV	Conventional ventilation
Fio_2	Fraction of inspired oxygen
HFJV	High-frequency jet ventilation
$Paco_2$	Partial pressure of carbon dioxide (arterial)
Pao_2	Partial pressure of oxygen
$\bar{P}aw$	Mean airway pressure
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
RDS	Respiratory distress syndrome

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Table I. Clinical data in two study groups

	Birth weight (kg)	Gestational age (wk)	Sex		Race		Transport	
			Male	Female	White	Black	Yes	No
Conventional ventilation (n = 20)	1.47 ± 0.35	30 ± 2	11	9	12	8	12	8
High-frequency jet ventilation (n = 20)	1.48 ± 0.24	30 ± 2	11	9	16	4	15	5

Data not included for one randomized but unpaired infant.

Although the precise pathophysiologic mechanisms underlying these forms of acute and chronic lung injury are still unclear, the use of high ventilatory pressures and the resultant barotrauma are thought to be major etiologic factors.[4,5]

Because the use of high ventilatory frequencies may allow adequate gas exchange at lower airway pressures than with conventional frequencies, high-frequency ventilation has been used as a rescue mode for infants in whom lung barotrauma has developed or assisted ventilation is failing.[6-11] Although HFV was successful in most infants in these studies, major airway complications have been reported.[11] Because early use of HFV may prevent development of barotrauma, other investigators, including ourselves, have utilized crossover study designs to evaluate this new ventilatory technique in infants during the early course of RDS.[12-16] These studies have compared blood gas values and ventilatory settings while alternating short periods (up to 4 hours) of HFV and conventional ventilation and observed potential benefits of high ventilatory frequencies. To determine the efficacy and safety of early intervention with high-frequency jet ventilation, we randomized infants with RDS to receive either HFJV or CV during the first day of life. Our results demonstrate that normal gas exchange may be accomplished during HFJV despite sustained reduction in mean airway pressure. Furthermore, we noted no increased incidence of complications associated with this mode of high-frequency ventilatory assistance.

METHODS

Patients were enrolled in the study between December 1, 1983, and January 31, 1986. During this period, 524 infants weighing between 1.0 and 2.0 kg were admitted to the intensive care nursery and screened. Within 24 hours of life, 85 of these infants required assisted ventilation (pressure-limited time-cycled) and met all of the following criteria: (1) $Pa_{O_2} \leq 90$ mm Hg; (2) $Pa_{CO_2} \geq 35$ mm Hg; (3) $Fi_{O_2} \geq 0.5$; (4) frequency ≥20/min; (5) PIP ≥20 cm H_2O; (6) PEEP ≥4 cm H_2O; (7) clinical and radiographic evidence of RDS; (8) no improvement in blood gas values at time of randomization. Forty-four infants who met the above criteria could not be randomized because of death before randomization (n = 13), use of a small (2.5 mm internal diameter) endotracheal tube during the first year of the study before introduction of small (19 gauge) catheters to measure endotracheal pressures (n = 9), sepsis (n = 8), severe congenital anomalies (n = 6), unavailability of an investigator or jet ventilator (n = 5), lack of parental consent (n = 2), and severe asphyxia (n = 1). Thus 41 infants were randomized to receive either HFJV or CV; the characteristics of the 40 infants who were paired are detailed in Table I. The protocol was approved by the Institutional Review Board, and informed consent was obtained for each infant after a detailed description of the study was given to the parents. Sedation (phenobarbital, morphine sulfate) or paralysis (pancuronium bromide) were not used routinely as part of the protocol, but were frequently ordered by the pediatric resident and attending neonatologist. Administration of each of these medications was comparable in both groups, and all but five infants given HFJV and four given CV received one or more of these medications during at least part of the 48-hour study period.

Ventilators and ventilatory management. Patients were randomized to receive either a pressure-limited time-cycled ventilator (BP-200 and Bear Cub, Bear Medical Systems, Inc., Riverside, Calif.; Sechrist Industries Inc., Anaheim, Calif.) or a high-frequency jet ventilator that has been previously described.[14,17] Patients who were randomized to receive CV (at 20 ± 6 hours) stayed on the pressure ventilator, but an algorithm was used to standardize changes in ventilator settings.[18] In a previous clinical study, ventilatory management consistent with this algorithm accelerated correction of arterial blood gas derangements when compared with control care.[19] Patients randomized to receive HFJV were switched to HFJV at 22 ± 7 hours. Initial ventilatory pressures during HFJV were selected by decreasing PIP and $\bar{P}aw$ approximately 20% and maintaining PEEP at the same level as during CV.[14] HFJV was used at a fixed frequency (250/min) and inspiratory/expiratory time ratio (1:3); an algorithm com-

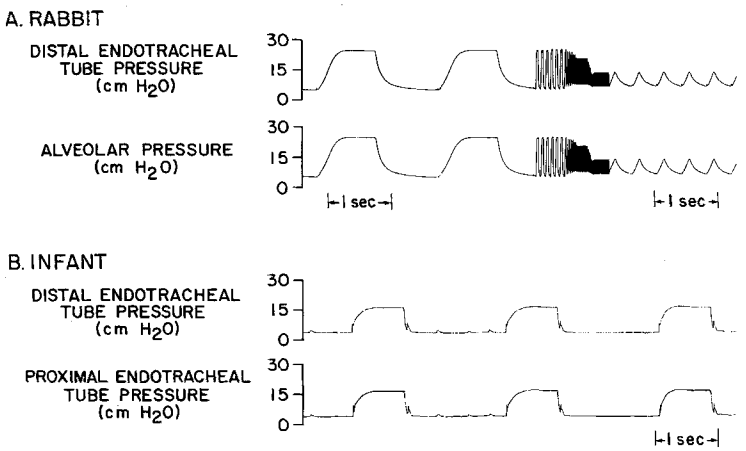

Fig. 1. Validation of techniques for pressure measurements used in study. **A,** Distal endotracheal tube and alveolar pressure recordings in adult rabbit during both conventional ventilation and high-frequency jet ventilation are essentially identical. **B,** Distal and proximal endotracheal tube pressures in infant during conventional ventilation are also identical.

parable to that used for CV was used to adjust PIP, $\bar{P}aw$, and PEEP. For both HFJV and CV algorithms, changes in pressure amplitude (PIP − PEEP) were used to control tidal volume delivery and hence $PaCO_2$; changes in frequency were performed only with CV. Changes in $\bar{P}aw$ and FiO_2 were used to adjust PaO_2. During both HFJV and CV, increase in $\bar{P}aw$ was used in hypoxic infants when FiO_2 was >0.70. Decrease in $\bar{P}aw$ was used during hyperoxia if FiO_2 was <0.40. Inability to maintain arterial blood gas values at $\bar{P}aw \leq 20$ cm H_2O and FiO_2 1.0 was used as a failure criterion. After 48 hours, infants receiving HFJV were switched back to CV, and subsequently both groups were managed with the CV algorithm.

Airway pressures, including PIP, $\bar{P}aw$, and PEEP during HFJV, were monitored via an air-filled 16- or 19-gauge polyvinyl catheter (Angiocath, Deseret Medical, Inc., Sandy, Utah) positioned inside the endotracheal tube, with the tip approximately 2 cm above the distal end of the endotracheal tube.[14] The pressure measuring system with the 19-gauge catheter was available only during the second year of the study. Because 16-gauge catheters markedly increase the resistance of 2.5 mm endotracheal tubes, infants with the small endotracheal tubes were not randomized during the first year of the study. Placement of the injector cannula at the proximal end of the endotracheal tube allowed accurate pressure measurements to be made near the distal end of the endotracheal tube. Pressure in the distal endotracheal tube is compared with alveolar pressure in an adult rabbit being switched from CV to HFJV (Fig. 1, *A*). Distal endotracheal tube pressures were obtained with a 16-gauge catheter. Alveolar pressures were measured with a piezoelectric transducer attached directly to an airtight capsule that was glued with cyanoacrylate to the pleural surface. Superficial incisions (about 2 mm deep) were performed on the pleural surface with a 22-gauge needle to assure communication with the distal airways or alveoli. Distal endotracheal tube and alveolar pressures (both PIP and PEEP) were virtually identical during HFJV at the frequency used in this study (Fig. 1, *A*). Because of the similar waveforms, endotracheal and alveolar $\bar{P}aw$ were also calculated to be the same. Recently, others have confirmed that endotracheal and alveolar $\bar{P}aw$ were also calculated to be the same. Recently, others have confirmed that endotracheal and alveolar $\bar{P}aw$ are also comparable during HFJV at 5 Hz (300/min).[20] Pressure measurement in the distal endotracheal tube allowed us to standardize a reference location for measuring the pressure input to the pulmonary system independent of the variable resistance of the different size endotracheal tubes used. The 16- or 19-gauge catheter was connected directly to a pressure transducer (Pneumogard 1230A, Novametrix Medical Systems, Inc., Wallingford, Conn.) to monitor the airway pressure waveform continuously. The in vitro frequency response of this system is flat for frequencies of up to 10 Hz.[21]

Equilibration of airway pressures occurs with pressure plateaus during CV; proximal endotracheal, distal endotracheal, and alveolar pressures in rabbits are identical (Fig. 1, *A*).[22] When distal and proximal endotracheal tube pressures are compared in an infant during CV, PIP, PEEP, and the pressure waveforms recorded from both sites are essentially identical (Fig. 1, *B*). Thus airway pressures during CV were recorded at the proximal endotracheal tube connector.

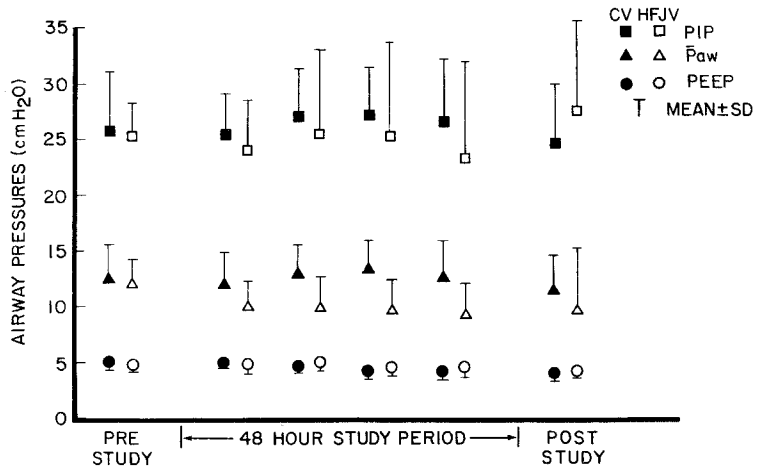

Fig. 2. Airway pressures (mean ± SD) during both control and four 12-hour study periods for infants in conventional *(CV)* and high-frequency jet ventilation *(HFJV)* groups. Airway pressures were comparable in both pre- and post-study periods. Analysis of variance of airway pressures revealed that mean air pressures *($\bar{P}aw$)* were lower ($P < 0.001$) in HFJV group, but peak inspiratory pressures *(PIP)* and positive end-expiratory pressures *(PEEP)* were comparable.

Table II. Ventilator settings and blood gas values during 6 hours before randomization

	Conventional ventilation	High-frequency jet ventilation
PIP (cm H_2O)	25.7 ± 5.1	25.0 ± 3.0
$\bar{P}aw$ (cm H_2O)	12.3 ± 3.0	11.9 ± 2.1
PEEP (cm H_2O)	4.9 ± 0.4	4.8 ± 0.6
Frequency (cpm)	27 ± 7	29 ± 8
I:E ratio	1:1.8 ± 0.6	1:1.8 ± 0.6
FiO_2	0.77 ± 0.15	0.73 ± 0.15
a/A O_2	0.187 ± 0.037	0.185 ± 0.049
$PaCO_2$ (mm Hg)	36.4 ± 4.2	38.2 ± 3.5
HCO_3 (mEq/L)	20 ± 1	20 ± 2

Transcutaneous oxygen (TCM_2, Radiometer A/S, Copenhagen) was continuously monitored during the 48-hour study period in both groups of patients. Intermittent blood gas determinations were performed as clinically indicated.

Study design and data analysis. Informed consent was obtained only after all criteria were met. Randomization was then performed according to weight stratification into two groups: 1.0 to 1.5 kg and 1.5 to 2.0 kg, utilizing sealed envelopes in blocks of six for each weight group. A subsequent block of six envelopes was added whenever only four envelopes were left in a weight group. The investigator obtaining consent was unaware of the odds of a subsequent infant falling into either treatment group.

To prospectively monitor the occurrence of major complications thought to be associated with assisted ventilation, sequential analyses of air leaks (pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium, and air embolism), progression of intraventricular hemorrhage, and mortality were performed[23]; in addition, sequential analysis of the combination of these complications was also performed. The presence of a complication would untie a pair, but mortality would override the presence of other complications in the combined analysis. These continuous analyses were used to assure early termination of the trial if large differences in complications occurred.

Blood gas results and corresponding air pressures were averaged over 6 hours both before and after the 48-hour study period and over 12-hour periods during the study, and expressed as mean ± SD. To compare the 6-hour pre- and post-study period data, paired t tests were used for within-group comparisons and unpaired t tests for between-group comparisons. Two-way analysis of variance for repeated measures was used for evaluation of the 12-hour periods of data during the 48-hour study period. Chi-square analysis was used to evaluate significance of categorical variables. $P < 0.05$ was considered statistically significant. Chest radiographs were performed before and after the 48-hour study period and when clinically indicated. These were reviewed by a pediatric radiologist without knowledge of the treatment group. Head ultrasound studies were also obtained before and after the 48-hour study period when thought to be clinically indicated by the attending neonatologist. When parental approval was obtained after extubation, bronchoscopy was

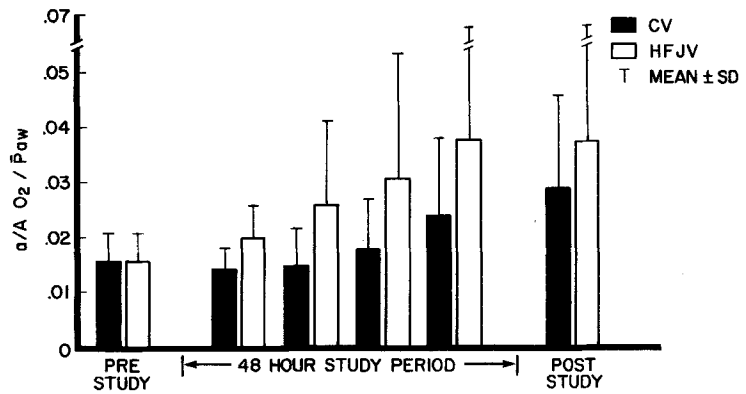

Fig. 3. Arterial/alveolar oxygen tension ratios corrected for mean airway pressure (mean ± SD) during both control and four 12-hour study periods for infants in conventional *(CV)* and high-frequency jet ventilation *(HFJV)* groups. Arterial/alveolar oxygen tension ratio corrected for mean airway pressure was comparable between groups during both pre- and post-study periods, but was improved during HFJV ($P < 0.05$).

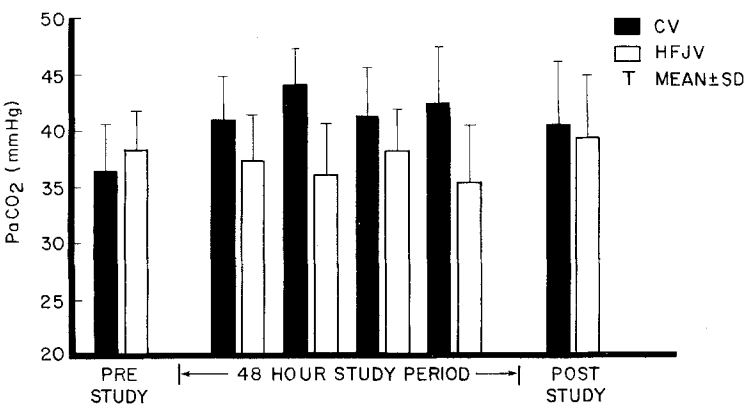

Fig. 4. $PaCO_2$ (mean ± SD) during both control and four 12-hour study periods for infants in conventional *(CV)* and high-frequency jet ventilation *(HFJV)* groups. $PaCO_2$ was comparable in both pre- and post-study periods, but significantly lower in HFJV group ($P < 0.001$).

performed by a pediatric pulmonologist who was unaware of the infant's treatment group.

RESULTS

Five infants did not complete the 48-hour period on the assigned ventilator: two infants in the HFJV group improved early, and assisted ventilation was discontinued, after 40 and 44 hours of HFJV, respectively; one infant in each group died before completion of the study period, after 12 and 23 hours of CV and HFJV, respectively; and one infant met the failure criteria, 27 hours into the study, and was crossed over from CV to HFJV.

During the 6-hour control period preceding randomization, ventilator settings and blood gas values were comparable in both HFJV and CV groups (Table II). During the 48-hour study period, infants receiving HFJV required a lower $\bar{P}aw$ than those receiving CV (analysis of variance, $P < 0.001$; Fig. 2). PIP and PEEP were comparable in both groups over the 48 hours ($P = 0.29$ and $P = 0.26$, respectively). Despite the reduction in $\bar{P}aw$ achieved with HFJV, the a/A O_2 was comparable in both groups (HFJV 0.28 ± 0.19, CV 0.21 ± 0.07, $P = 0.42$). In both groups there was a significant effect of time on a/A O_2 (both $P < 0.001$) during the 48 hours of the study, consistent with improving oxygenation. Inasmuch as $\bar{P}aw$ was reduced in infants receiving HFJV, a/A O_2 corrected for $\bar{P}aw$ (a/A $O_2/\bar{P}aw$) was improved in these infants ($P < 0.05$, Fig. 3). $PaCO_2$ was lower in the HFJV group ($P < 0.001$, Fig. 4), whereas HCO_3 was comparable in both groups (HFJV 19.2 ± 1.4, CV 19.7 ± 1.6 mEq/L, $P = 0.43$). Consequently, pH was lower in the infants receiving CV (7.29 ± 0.03 vs 7.34 ± 0.03, $P < 0.001$).

Table III. Major complications

	Air leaks*	Intraventricular hemorrhage*	Deaths*	Total deaths	Bronchopulmonary dysplasia	Necrotizing tracheobronchitist
Conventional ventilation (n = 20)	8	4/15	1	3	4	0/7
High frequency jet ventilation (n = 20)	4	3/18	1	3	3	1/10

*During 48-hour study period.
†At bronchoscopy or autopsy.

During the 48-hour study period, one or more air leaks occurred in eight infants in the CV group and in four infants in the HFJV group (P = 0.11, Table III). Specific air leaks during HFJV versus CV were: pneumothorax three versus six, pulmonary interstitial emphysema one versus four, pneumomediastinum two versus two, and pneumopericardium none versus one. The incidence of intraventricular hemorrhage over the 48-hours was comparable. In five patients in the CV group and two in the HFJV group, we were unable to determine if progression of intraventricular hemorrhage occurred during the 48-hour period because repeated head ultrasound studies were discouraged by the attending neonatologist.

Mortality during the 48-hour study period, subsequent mortality, and incidence of bronchopulmonary dysplasia (defined as supplemental oxygen requirement beyond 28 days of life with abnormal radiographic findings) were also comparable between groups (Table III). Both infants who died during the 48-hour study had respiratory failure complicated by grade IV intraventricular hemorrhage. Two infants randomized to CV subsequently died, at 7 and 17 days, respectively, of respiratory failure. Two infants randomized to HFJV subsequently died, at 16 and 17 days of age, respectively, one of respiratory failure and the other of complications of necrotizing enterocolitis. Median duration of oxygen supplementation and assisted ventilation were 11.6 and 6.5 days, respectively, for CV infants and 11.0 and 5.5 days for HFJV infants. Bronchoscopies performed on five infants in the CV group and eight in the HFJV group did not reveal evidence of necrotizing tracheobronchitis. There were no gross pathologic changes in the trachea in the four nonsurvivors at autopsy (two in each treatment group), but the infant who had been randomized to HFJV and died during the 48-hour study period had microscopic evidence of necrotizing tracheitis with sloughing of the respiratory mucosa. The survivors are currently being evaluated as part of a comprehensive follow-up program. To date, their ages range from 5 to 31 months, and no major differences in outcome have been found between the control and experimental groups.

DISCUSSION

This randomized trial demonstrates that HFJV over a 48-hour period results in a sustained reduction in $\bar{P}aw$ without compromise of gas exchange. We found no evidence for increased side effects secondary to HFJV, although with our relatively small patient population, we were unable to detect a significant reduction in the major complications associated with assisted ventilation.

Several new modes of assisted ventilation have been developed; all are characterized by higher than usual frequencies and smaller than usual tidal volumes. Of these, HFJV has undergone the most extensive clinical use,[24] although in recent years extensive research has been completed using high-frequency oscillation. Controlled clinical experience in infants with RDS using HFJV,[14,15] high-frequency oscillation,[13] and high-frequency positive-pressure ventilation[12,16] suggests that these techniques may reduce barotrauma. High-frequency positive-pressure ventilation[12,16] and high-frequency oscillation[13] allow reduction of PIP and airway pressure swings; HFJV has additionally permitted reduction in $\bar{P}aw$ with maintenance of normal blood gas values.[14] It is possible that mechanisms of enhanced gas exchange that occur during high-frequency oscillation[25] are involved in the maintenance of oxygenation at lower $\bar{P}aw$ during HFJV. It is also possible that, because the reduction in $\bar{P}aw$ is related primarily to the low ratio of inspiratory to expiratory times typically employed during HFJV, oxygenation may not be as impaired as it would be if PIP or PEEP were markedly reduced.[26] We have previously shown that the duration of inspiratory and expiratory times allowed by the combination of frequency (250/min) and I:E ratio (1:3) used in this trial is appropriate for the prevention of air trapping and reduction of airway pressures in both normal and surfactant-deficient lungs.[21] It is likely that PIP and airway pressure swings are also important in producing either acute or chronic barotrauma and that other high-frequency ventilators may also be beneficial in preventing the risk for lung injury.

The development of necrotizing tracheobronchitis has

been associated with HFJV,[8] particularly when inappropriate humidification is used.[27] We used a heating and humidification system that provides gases with very high water saturation without water particles.[17] Thus the incidence of tracheal lesions associated with HFJV in our study (microscopic injury in one infant at autopsy) is much lower than the 44% previously reported in infants receiving HFJV for a mean of 48 hours.[11] Although adequate humidification and temperature of gases are important in the prevention of tracheal lesions, it is possible that damage may be caused by the other forms of physical trauma, such as high flow of gases and water particles.

The selection criteria were designed to enroll infants with severe RDS and exclude patients with other confounding diseases. Very low birth weight infants (<1.0 kg) were excluded because of the high mortality and morbidity unassociated with the pulmonary disease that is prevalent in this patient population. It is possible that HFJV may be most beneficial in very small infants who are at high risk for chronic lung disease, but the number of infants in this study does not allow evaluation of the effect of weight on the outcome variables.

We initiated HFJV relatively early in the clinical course of RDS, as compared with previous rescue studies, because we wanted to determine if it could prevent barotrauma. The initial period of CV allowed enough time to stabilize the infants, determine qualifications according to enrollment criteria, and obtain informed consent. The 48-hour limit of this study was selected because the natural history of RDS is such that by the third day of life improvement frequently occurs. It is possible, however, that still earlier or exclusive use of HFJV may be more beneficial in the prevention of acute and chronic barotrauma than the protocol used in this trial.

The study sample was large enough to detect significant differences in airway pressures and gas exchange between the two modes of assisted ventilation. With a sequential design, as few as seven untied pairs favoring the same treatment would have detected a difference between treatment modes. Nonetheless, we are limited in our ability to make definite conclusions regarding major complications associated with ventilatory therapy because the various side effects occurred in both treatment groups. It is clear from our data that HFJV does not eliminate barotrauma as manifested by the development of air leaks.

This study thus demonstrates that HFJV may be safely used in infants with severe RDS, and does not adversely alter their clinical course. Furthermore, HFJV was superior to CV in accomplishing gas exchange during the acute stage of RDS. Larger trials using HFJV as the sole mode of assisted ventilation are needed to determine if the morbidity and mortality associated with barotrauma may be reduced.

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