Multicenter Controlled Clinical Trial of High-frequency Jet Ventilation in Preterm Infants With Uncomplicated Respiratory Distress Syndrome

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ABSTRACT. *Objective.* **To test the hypothesis that high-frequency jet ventilation (HFJV) will reduce the incidence and/or severity of bronchopulmonary dysplasia (BPD) and acute airleak in premature infants who, despite surfactant administration, require mechanical ventilation for respiratory distress syndrome.**

Design. **Multicenter, randomized, controlled clinical trial of HFJV and conventional ventilation (CV). Patients were to remain on assigned therapy for 14 days or until extubation, whichever came first. Crossover from CV to HFJV was allowed if bilateral pulmonary interstitial emphysema or bronchopleural fistula developed. Patients could cross over to the other ventilatory mode if failure criteria were met. The optimal lung volume strategy was mandated for HFJV by protocol to provide alveolar recruitment and optimize lung volume and ventilation/perfusion matching, while minimizing pressure amplitude and O_2 requirements. CV management was not controlled by protocol.**

Setting. **Eight tertiary neonatal intensive care units.**

Patients. **Preterm infants with birth weights between 700 and 1500 g and gestational age <36 weeks who required mechanical ventilation with F_{IO_2} >0.30 at 2 to 12 hours after surfactant administration, received surfactant by 8 hours of age, were <20 hours old, and had been ventilated for <12 hours.**

Outcome Measures. **Primary outcome variables were BPD at 28 days and 36 weeks of postconceptional age. Secondary outcome variables were survival, gas exchange, airway pressures, airleak, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and other nonpulmonary complications.**

Results. **A total of 130 patients were included in the final analysis; 65 were randomized to HFJV and 65 to CV. The groups were of comparable birth weight, gestational age, severity of illness, postnatal age, and other demographics. The incidence of BPD at 36 weeks of postconceptional age was significantly lower in babies randomized to HFJV compared with CV (20.0% vs 40.4%). The need for home oxygen was also significantly lower in infants receiving HFJV compared with CV (5.5% vs 23.1%). Survival, incidence of BPD at 28 days, retinopathy of prematurity, airleak, pulmonary hemorrhage, grade I–II IVH, and other complications were similar. In retrospect, it was noted that the traditional HFJV strategy emphasizing low airway pressures (HF-LO) rather than the prescribed optimal volume strategy (HF-OPT) was used in 29/65 HFJV infants. This presented a unique opportunity to examine the effects of different HFJV strategies on gas exchange, airway pressures, and outcomes. HF-OPT was defined as increase in positive end-expiratory pressure (PEEP) by ≥1 cm H_2O from pre-HFJV baseline and/or use of PEEP of ≥7 cm H_2O. Severe neuroimaging abnormalities (PVL and/or grade III–IV IVH) were not different between the CV and HFJV infants. However, there was a significantly lower incidence of severe IVH/PVL in HFJV infants treated with HF-OPT compared with CV and HF-LO. Oxygenation was similar between CV and HFJV groups as a whole, but HF-OPT infants had better oxygenation compared with the other two groups. There were no differences in P_{aCO_2} between CV and HFJV, but the P_{aCO_2} was lower for HF-LO compared with the other two groups. The peak inspiratory pressure and ΔP (peak inspiratory pressure-PEEP) were lower for HFJV infants compared with CV infants.**

Conclusions. **HFJV reduces the incidence of BPD at 36 weeks and the need for home oxygen in premature infants with uncomplicated RDS, but does not reduce the risk of acute airleak. There is no increase in adverse outcomes compared with CV. HF-OPT improves oxygenation, decreases exposure to hypocarbia, and reduces the risk of grade III–IV IVH and/or PVL.** *Pediatrics* **1997;100: 593–599;** ***high-frequency ventilation, outcome, bronchopulmonary dysplasia, multicenter clinical trial, intraventricular hemorrhage, hypocarbia.***

ABBREVIATIONS. HFJV, high-frequency jet ventilation; RDS, respiratory distress syndrome; PIE, pulmonary interstitial emphysema; BPD, bronchopulmonary dysplasia; CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; F_{IO_2}, fraction of inspired oxygen; PCA, postconceptional age; $\overline{Paw}$, mean airway pressure; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; IMV, intermittent mandatory ventilation; ΔP, pressure amplitude; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; HF-LO, low airway pressure strategy; HF-OPT, optimal volume strategy.

With adequate documentation of the safety and effectiveness of high-frequency jet ventilation (HFJV) in rescue situations,[1–4] attention has shifted to earlier use of this technique in infants with severe respiratory distress syndrome (RDS) not yet complicated by airleak. The goal of early intervention is to reduce the incidence of

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chronic lung disease. A previous collaborative study showed that patients with pulmonary interstitial emphysema (PIE) who were treated with HFJV had a 25% lower incidence of bronchopulmonary dysplasia (BPD) compared with those treated with conventional ventilation (CV).[3] Although this difference was not statistically significant, the lateness of the intervention (~48 hours of age) may have reduced the efficacy of HFJV in preventing BPD. High-frequency oscillatory ventilation (HFOV), a related technique, has been reported to reduce the incidence of BPD in infants with RDS when a strategy aimed at optimizing lung volume is used.[5,6] However, there are limited data available regarding the use of HFJV in infants with uncomplicated RDS. Additionally, there is considerable debate regarding the appropriate ventilatory strategy to use; however, recent animal data clearly demonstrate that lung volume recruitment and avoidance of atelectasis reduces lung injury and improves surfactant function.[7]

The purpose of our study was to test the hypothesis that early use of HFJV in infants with uncomplicated RDS reduces the incidence of airleak and BPD.

PATIENTS AND METHODS

Patient Selection

Patients with birth weight between 700 and 1500 g and gestational age of <36 weeks were eligible for entry into the study if they required mechanical ventilation with F_{IO_2} ≥0.30 at 2 to 12 hours after surfactant administration, received surfactant by 8 hours of age, were <20 hours old, and had been mechanically ventilated for <12 hours. Exclusion criteria were respiratory failure attributable to disease other than radiographically confirmed RDS, P_{aCO_2} <30 Torr and/or P_{aO_2} >100 Torr, significant bilateral PIE, major congenital anomalies, <24 weeks' gestation (believed to be previable), neuromuscular disease affecting respiration, and multiple births of three or more.

Study Design and Sample Size

The study protocol was approved by the Institutional Review Board of each participating center. After obtaining informed consent, eligible patients were stratified by birth weight (700 to 1000 g, 1001 to 1250 g, and 1251 to 1500 g) and assigned to HFJV or to continued CV, using a separate table of random numbers for each of the three stratification groups to ensure balanced allocation to the two arms of the study. Treatment assignments based on the random numbers table were placed in sequentially numbered opaque envelopes in blocks of 10 per stratification group per center. Primary outcome variables were BPD at 28 days and at 36 weeks' postconceptional age (PCA). Secondary outcome variables were survival, gas exchange, airway pressures, airleak and other complications. The definitions of BPD used were 1) need for oxygen or mechanical ventilation with compatible radiographic changes at 28 days, and 2) requirement for oxygen or mechanical ventilation at 36 weeks' PCA. The assigned mode of ventilation was to be maintained until the infant was extubated or for 14 days, whichever came first. Some centers elected to limit the original assignment period to 7 days because of limited jet ventilator availability. Infants assigned to CV who developed significant bilateral PIE or persistent bronchopleural fistula were permitted to cross over to HFJV because of the previously demonstrated efficacy of HFJV for these conditions.[3,4] Patients in either arm of the study who were failing the assigned therapy were allowed to cross over to the other ventilatory mode. Failure was defined as an inability to maintain P_{aO_2} ≥40 Torr and/or pH ≥7.20 despite mean airway pressure ($\overline{P_{aw}}$) of 18 cm H_2O. Success was defined as sustained improvement in gas exchange such that failure criteria were no longer met. Once extubated, if an infant required reintubation before 14 days of age for apnea only, CV was used regardless of initial assignment. The infant was returned to the ventilatory mode assigned originally if significant respiratory disease still was present.

Analysis of statistical power was based on an α level of 0.05, 1-β of 0.80, a moderate treatment effect, and estimated baseline incidence of chronic lung disease of 40% to 60%. Thus, using a two-sided test, an estimated 200 patients would be needed to detect, with 80% probability, a difference of 20 percentage points in the incidence of BPD.

Data Collection and Analysis

After randomization, all babies were reintubated with the triple lumen Hi-Lo endotracheal tube (Mallinkrodt Medical, St Louis, MO) so that airway pressures could be monitored near the tip of the endotracheal tube in both groups. Airway pressures were monitored using either the built-in airway pressure monitor of the Life Pulse Jet ventilator or the free-standing Bunnell Ventilator Monitor (both by Bunnell Inc, Salt Lake City, UT). Both devices sample airway pressures every 1 to 2 milliseconds and have been shown to have an adequate response over the clinically applicable range of frequencies.

After reintubation, baseline airway pressures, vital signs, and blood gas values were recorded while still on prestudy CV settings, and only then was HFJV initiated. Airway pressures, blood gases, and vital signs were recorded at 2, 6, and 12 hours, every 24 hours for 72 hours, and at 7 and 14 days. A chest radiograph was obtained at the time of initial reintubation. Subsequent radiographs were obtained as clinically indicated. Cranial sonograms were obtained as part of routine care on days 1 to 3 and again at approximately day 7 of life. Subsequent cranial ultrasound studies were performed at 4 to 6 weeks of age and/or before discharge. Additional studies were performed only as clinically indicated. A cranial sonogram before entry was not required because of early entry, and thus possible preexisting abnormalities could not be documented. Echocardiograms were obtained only when clinically indicated for suspected patent ductus arteriosus. Length of supplemental oxygen and ventilator requirement, use of steroids, occurrence of complications, and final outcome were obtained from the medical record at the time of discharge or death.

Blood gas, airway pressure, and other normally distributed continuous variables were analyzed by analysis of variance for repeated measures with post hoc Scheffe test, two-tailed unpaired *t* test, and analysis of variance, as appropriate. Data that were not normally distributed (duration of oxygen requirement and ventilator support, length of hospitalization) were analyzed using the Mann–Whitney *U* test. Categorical variables were analyzed by χ^2 and Fisher's exact probability tests. Patients were analyzed according to initial assignment, regardless of possible subsequent crossover (intent to treat analysis).

Ventilators and Ventilator Strategies

Patients assigned to HFJV were ventilated with the Life Pulse high-frequency jet ventilator (Bunnell Inc). This device senses airway pressures near the tip of the endotracheal tube, and a microprocessor servocontrols driving gas pressure to maintain the desired peak inspiratory pressure (PIP).[8] A conventional ventilator used in tandem with the Life Pulse is a source of bias flow of heated, humidified gas of the same F_{IO_2} as the jet ventilator. The conventional ventilator generates positive end-expiratory pressure (PEEP) and provides intermittent sigh breaths in the form of background intermittent mandatory ventilation (IMV). Standard time-cycled, pressure-limited infant ventilators were used for CV.

Because RDS is characterized by diffuse microatelectasis, the study protocol specifically recommended an optimal volume strategy (HF-OPT) designed to provide alveolar recruitment, optimize lung volume, and improve ventilation/perfusion matching, while minimizing F_{IO_2} and pressure amplitude (ΔP = PIP–PEEP). This approach has been used extensively with HFOV[9,10] and was validated with HFJV in an unpublished pilot study. The background IMV at a rate of two to five breaths per minute with inspiratory time of 0.5 to 0.8 seconds on the conventional ventilator serves to recruit lung volume, and adequate $\overline{P_{aw}}$ is used to maintain lung inflation. Relatively high PEEP is thought to be safe with HFJV because of the low PIP and ΔP. Volume recruitment is accomplished by initially maintaining PIP the same as on CV and increasing the PEEP to 6 to 8 cm H_2O when HFJV is first started. This maneuver typically raises the $\overline{P_{aw}}$ 0.5 to 2 cm H_2O above pre-HFJV baseline. Once the initial recruitment is accomplished

(as manifested by improving oxygen saturation and chest wall movement), the PIP must be weaned rapidly to avoid hypocarbia that would otherwise develop as a consequence of improved lung compliance resulting from normalization of lung volume. To avoid recurrence of atelectasis, the F_{IO_2}, rather than $\overline{Paw}$, should be weaned in response to improving oxygenation until the F_{IO_2} falls to <0.4. As PIP is weaned in response to improving ventilation, the PEEP is increased slightly to maintain $\overline{Paw}$ at the desired level.

No attempt was made to control CV management. However, the approach to CV in premature infants with significant RDS was fairly uniform in the participating centers and consisted of ventilator rates of 30 to 60 breaths per minute, short inspiratory times of 0.3 to 0.4 seconds, PEEP of 4 to 6 cm H_2O, and PIP sufficient to achieve adequate tidal volume. The target blood gas values in both groups were similar: pH, 7.25 to 7.40, $Paco_2$, 35 to 45 Torr, and Pao_2, 50 to 80 Torr.

General Supportive Neonatal Care

Infants received neonatal care in accordance with standard practice in the respective neonatal intensive care units. All received exogenous surfactant (Exosurf Neonatal, Burroughs Wellcome Co, Research Triangle Park, NC or Survanta, Ross Product Division, Abbott Laboratories, Columbus, OH) before entry, and subsequent doses were given according to the manufacturer's recommendations. The use of systemic steroids to treat evolving chronic lung disease was permitted after 14 days of age. No attempt was made to control nonrespiratory aspects of care. Muscle relaxants were seldom given, and their use was at the discretion of the clinician. Symptomatic patent ductus arteriosus was treated with indomethacin or surgical ligation. Hypotension was treated with volume expansion and inotropic agents at the discretion of the clinical team.

Early Study Termination and Post Hoc Analysis of the Effect of Strategy

Patient enrollment was terminated in the fall of 1995, after 144 infants were entered in the study, for the following reasons:

1. Safety concerns were raised by the recent report of higher incidence of adverse outcomes (grade III–IV intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], or death) associated with HFJV used with the low pressure strategy in a similar population.[11]
2. Interim analysis revealed that the traditional HFJV strategy emphasizing low airway pressures (the low pressure strategy; HF-LO) rather than the prescribed HF-OPT was used in a substantial portion of the infants in the present study.

Although the comparison of HF-OPT versus HF-LO was not part of the original study design, the protocol violations presented a unique opportunity to examine the effects of different jet ventilator strategies on gas exchange, airway pressures, and outcomes. For this analysis, compliance with HF-OPT was defined as an increase in PEEP by ≥1 cm H_2O from pre-HFJV baseline and/or use of PEEP of ≥7 cm H_2O.

RESULTS

Of the 144 patients entered into the study at nine centers, 14 patients (all patients from one center) were excluded from this report, because they had been entered simultaneously into another similar study and reported elsewhere.[11] Thus, 130 patients from eight centers remained for analysis; 65 were randomized to HFJV and 65 to CV. The two groups were comparable in terms of birth weight, gestational age, age at entry into the study, and other demographics (Table 1). The severity of their illness as determined by ventilator settings and arterial blood gases at entry into the study was also similar (Table 2). Likewise, there were no significant differences between the HFJV subgroups in demographics or in severity of initial illness.

All site principal investigators had at least 4 years' experience with HFJV before their participation in the study. Adherence to prescribed ventilator strategy ranged from 17% to 65% of patients in the eight centers and did not correlate with the investigator's length of experience with HFJV. Being treated in a specific center was not an independent predictor of any of the major outcome variables (survival, neurologic outcome, or BPD).

BPD, Survival, and Complications

The incidence of BPD, as defined by continued oxygen or ventilator dependence at 36 weeks' PCA, was significantly lower in babies assigned to HFJV compared with CV (20.0% vs 40.4%, $P = .037$, odds ratio = 0.37, 95% confidence interval (CI) = 0.14–0.94) (Table 3). The need for home oxygen in the HFJV patients was much lower than for CV infants (5.5% vs 23.1%, $P = .019$, odds ratio = 0.19, 95% CI = 0.04–0.81), although duration of supplemental oxygen *while hospitalized* was not significantly different between the two groups. Survival and incidence of BPD at 28 days were comparable in the two groups (Table 3). The use of steroids for treatment of chronic lung disease was similar (21% for HFJV and 30% for CV). The total length of hospitalization and need for assisted ventilation were not significantly different between the two groups (Table 3). Crossover to the other arm of the study occurred in 33% of CV patients and 5% of HFJV patients ($P = .0001$). Crossover was successful in 67% of patients switched from CV to HFJV and 0% of those switched from HFJV to CV ($P = .06$).

Incidence of retinopathy of prematurity, airleak, pulmonary hemorrhage, grade I–II IVH, and other complications was similar (Table 4). Severe neuroimaging abnormalities (PVL and/or grade III–IV IVH) were not significantly different between CV and HFJV. However, there was a significantly lower in-

TABLE 1. Patient Demographics

	CV (N = 65)	HF (N = 65)	HF-OPT (N = 36)	HF-LO (N = 29)
BW (g)	1021 ± 203	1019 ± 224	1043 ± 239	990 ± 203
GA (wk)	27.4 ± 2.0	27.3 ± 2.1	27.3 ± 2.2	27.3 ± 1.9
Male/female (% male)	38/27 (58.5)	39/26 (60)	24/12 (66.7)	15/14 (51.7)
Inborn/outborn (% inborn)	50/15 (76.9%)	49/16 (75.4)	31/5 (86.1)	18/11 (62.1%)
Apgar, 1 minute	4 (1–9)	3.5 (0–8)	4 (1–8)	3 (0–7)
Apgar, 5 minutes	7 (2–10)	7 (1–9)	7 (1–9)	7 (1–9)
Age at entry (hours)	8.3 ± 4.2	8.1 ± 4.2	7.9 ± 4.5	8.4 ± 3.8

HF-HI indicates the optimal volume strategy group; HF-LO, the low-pressure strategy group Birth weight (BW), gestational age (GA), and age at entry are expressed as mean ± SD. Apgar scores at 1 and 5 minutes are expressed as median (range). All P values > 0.1.

TABLE 2. Baseline Ventilator Settings and Blood Gas Values

	CV (N = 65)	HF (N = 65)	HF-OPT (N = 36)	HF-LO (N = 29)
Fio_2	68.7 ± 24.9	61.8 ± 22.7	64.0 ± 24.3	59.1 ± 20.8
PIP (cm H_2O)	24.4 ± 5.1	24.3 ± 5.0	25.4 ± 5.6	23.0 ± 3.8
PEEP (cm H_2O)	4.9 ± 1.0	4.9 ± 0.9	4.8 ± 1.1	4.9 ± 0.6
$\overline{Paw}$ (cm H_2O)	10.0 ± 3.1	10.0 ± 2.6	10.2 ± 3.0	9.8 ± 2.2
IMV (breaths/min)	47.5 ± 17.7	43.9 ± 15.7	44.4 ± 17.6	43.4 ± 13.3
Pao_2 (torr)	70.4 ± 29.1	73.0 ± 36.8	74.2 ± 43.1	71.5 ± 27.3
$Paco_2$ (torr)	41.4 ± 8.5	40.3 ± 8.8	41.0 ± 9.5	39.3 ± 7.8

Data are expressed as mean ± SD. All *P* values not significant.

TABLE 3. Major Outcomes

	CV (N = 65)	HF (N = 65)	HF-OPT (N = 36)	HF-LO (N = 29)
Surv. 36 wk	52/65 (80)	55/65 (84.6)	29/36 (80.6)	26/29 (89.7)
BPD 28d	37/52 (71.2)	37/55 (67.3)	20/29 (69.0)	17/26 (65.4)
BPD 36 wk	21/52 (40.4)	11/55 (20.0)*	6/29 (20.7)	5/26 (19.2)
Steroids	10/33 (30.3)	6/28 (21.4)	3/14 (21.4)	3/14 (21.4)
Home O_2	12/52 (23.1)	3/55 (5.5)†	1/29 (3.4)	2/26 (7.7)
Days O_2	46 (3–167)	37 (3–160)	32 (3–103)	45 (3–160)
Vent. days	26 (2–82)	20 (3–96)	20 (3–96)	20 (3–86)
Hosp. days	76 (33–167)	71 (24–198)	70 (40–156)	71.5 (24–198)
Crossover	21/65 (32.3)	3/65 (4.6)‡	1/36 (2.8)	2/29 (6.9)
Success after crossover	14/21 (66.7)	0/3 (0)§	0/1 (0)	0/2 (0)

* $P = .037$ vs CV, odds ratio = 0.37, 95% CI = 0.14–0.95.
† $P = .019$ vs CV, odds ratio = 0.19, 95% CI = 0.04–0.81.
‡ $P < .0001$ vs CV, odds ratio = 0.10, 95% CI = 0.03–0.39.
§ $P = 0.06$ vs CV.
Surv. 36 wk indicates survival to 36 weeks' PCA; BPD 28d, incidence of BPD at 28 days in survivors; BPD 36 wk, BPD at 36 wk PCA in survivors; Steroids, use of systemic steroids for treatment of evolving or established BPD; Home O_2, need for home supplemental oxygen; Days O_2, duration of supplemental oxygen in surviving patients; Vent. days, duration of assisted ventilation (including CPAP) in surviving patients; Hosp. days, total duration of hospitalization in surviving patients. Data are expressed as number of confirmed outcomes/number of patients at risk for whom data are available, and (%), or as median (range).

cidence of severe neuroimaging abnormalities in HFJV infants treated with HF-OPT compared with CV and HF-LO (Table 4). When undesirable outcomes (severe grades of IVH or PVL, or death) were combined into a single outcome measure, there were no significant differences among the three groups (Table 4).

Because of the remote possibility that the 53 g difference between the two HFJV groups, despite being statistically insignificant ($P = .35$), could influence the frequency of IVH and PVL, we reanalyzed the data using stepwise logistic regression to examine the effect of birth weight on major outcomes. There was a predictable effect on survival and BPD, but there was no improvement in the discriminant power of the model with respect to the incidence of IVH/PVL when birth weight was added.

Gas Exchange and Airway Pressures

Oxygenation, expressed as arterial/alveolar Po_2 ratio, was similar between CV and HFJV as a whole, but secondary analysis revealed significantly improved oxygenation with HF-OPT compared with the other two groups (see Figure, panel A). The differences in the efficiency of oxygenation were reflected in a lower Fio_2 requirement in the HF-OPT group compared with the HF-LO group (see Figure, panel B). There were no significant differences in $Paco_2$ over the course of the first 24 hours between CV and HFJV, but the $Paco_2$ was lower in the HF-LO subgroup compared with the other two groups (see Figure, panel C). By design, mean airway pressure was initially higher in the HF-OPT group. By 12 hours, the difference was no longer significant, and the $\overline{Paw}$ was declining in parallel with the other two groups (see Figure, panel D). The PIP and ΔP were significantly lower for HFJV infants compared with CV infants (Figure, panels E and F). The ΔP tended to be lower in the optimal volume group because of higher PEEP, but the difference between the two HFJV groups was not significant. At 48 hours after entry into the study, the HFJV infants still had significantly lower PIP (16.3 ± 5.0 vs 20.0 ± 4.5 cm H_2O; $P < .001$), compared with CV, whereas the Fio_2 was similar. At 7 days after entry, the PIP in infants still requiring intubation remained significantly lower in HFJV compared with CV infants (14.6 ± 2.6 vs 17.6 ± 5.7 cm H_2O, $P < .05$). The Fio_2 at 7 days after entry was also lower in HFJV compared with CV infants (0.27 ± 0.07 vs 0.33 ± 0.14; $P <. 02$).

DISCUSSION

This study adds to the growing body of evidence that high-frequency ventilation can reduce the incidence and/or severity of chronic lung disease when used early in the course of RDS.[5,6] This is the first report that demonstrates such a reduction can be achieved using HFJV. Given the extreme degree of prematurity of infants entered into this study, it is not unexpected that the incidence of BPD, as traditionally defined at 28 days of age, is high regardless of group assignment. At the extremes of prematurity, anatomic immaturity of the lung, rather than lung injury, may be responsible for oxygen requirement at 28 days. Furthermore, although this study was designed as an early-intervention trial, babies still had to demonstrate established RDS despite surfactant replacement and were enrolled at a mean age of ~8 hours, an age by which the lung injury sequence has already become well established.[9] The definition of BPD as oxygen requirement at 36 weeks' PCA is becoming increasingly accepted as a more important measure of respiratory outcome than the traditional 28-day definition.[12,13] Shennan et al showed that oxygen requirement at 36 weeks' PCA was a better predictor of pulmonary status at 2 years of age.[14] Although the differences in BPD at 36 weeks PCA did not translate into shorter hospitalization, the greater need for home oxygen implies greater overall resource use and may imply higher risk of rehospitalization. The failure to demonstrate decreased incidence of airleak is somewhat surprising. Interestingly, the HF-LO group tended to have less airleak compared with both CV and the optimal volume HFJV group. It remains to be seen whether this is a function of inexperience with HF-OPT or is inherent in the technique.

Unlike Wiswell et al,[11] we did not see an increased incidence of severe neurosonographic abnormalities

TABLE 4. Major Complications

	CV (N = 65)	HF (N = 65)	HF-OPT (N = 36)	HF-LO (N = 29)
IVH gr. I, II	26/59 (44.1)	26/61 (42.6)	15/34 (44.1)	11/27 (40.7)
IVH gr. III, IV	9/59 (15.3)	9/61 (14.8)	3/34 (8.8)	6/27 (22.2)
PVL	9/58 (15.5)	4/61 (6.6)	0/34 (0)	4/27 (14.8)
Sev IVH and/or PVL	16/58 (27.6)	12/61 (19.7)	3/34 (8.8)*	9/27 (33.3)
Pulm. hemorrhage	6/61 (9.8)	4/64 (6.3)	2/35 (6.1)	2/29 (6.9)
PDA	47/60 (78.3)	45/64 (70.3)	26/35 (72.7)	19/29 (65.5)
NEC	3/59 (5.1)	10/63 (15.9)	8/35 (22.9)	2/28 (7.1)
ROP	22/51 (43.1)	24/54 (44.4)	10/29 (34.5)	14/25 (56.0)
Airleak	23/65 (35.4)	18/65 (27.7)	12/36 (33.3)	6/29 (20.7)
Poor outcome	26/65 (40.0)	20/65 (30.8)	9/36 (25.0)	11/29 (37.9)

* $P = .048$ for three-way comparison of HF-OPT, CV, and HF-LO.
$P = .039$, odds ratio = 0.19, 95% CI = 0.04–0.94 for HF-OPT vs HF-LO.
$P = .062$, odds ratio = 0.25, 95% CI = 0.05–1.05 for HF-OPT vs CV.
Data are expressed as number of confirmed diagnoses/number of patients at risk for whom data are available, and (%). PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity (any stage); Airleak, pneumothorax and/or pulmonary interstitial emphysema and/or pneumomediastinum and/or pneumopericardium; Sev IVH and/or PVL, grade III–IV IVH and/or PVL; Poor outcome, grade III–IV IVH, PVL, or death.

in infants receiving HFJV. Even infants treated with the low volume strategy similar to that used by Wiswell et al[11] were not significantly different from those receiving CV in our study. However, when compared with HF-OPT patients, there was an increased incidence of neurosonographic abnormalities in the group treated with HF-LO. In view of Graziani's recent findings of an association among hypocapnia with CV and periventricular cysts, grade III–IV IVH, and cerebral palsy,[15] and a subsequent study from the same institution demonstrating the same phenomenon with HFJV,[16] we speculate that the differences found in our study may be related to the greater exposure to hypocapnia in the HF-LO group. A similar association of hypocarbia and PVL in premature infants was reported by Calvert et al[17] and Fujimoto et al.[18] Likewise, data from patients with persistent pulmonary hypertension subjected to conventional hyperventilation suggest increased risk of adverse neurodevelopmental outcome and sensorineural hearing loss with marked hypocapnia.[19,20] The presumptive mechanism underlying these effects are the $Paco_2$-related alterations in cerebral blood flow.[21]

Concerns about possible association of high-frequency ventilation with adverse neurologic outcome date back to the collaborative National Institutes of Health-sponsored HIFI Study of oscillatory ventilation, which showed a significant increase in severe IVH and PVL, as well as airleak, postextubation atelectasis, need for vasopressors, and crossover to the other ventilatory mode in the high-frequency group.[22] It has been speculated that the poor results were the consequence of failure to emphasize volume recruitment and maintenance.[23] Unfortunately, no data are available regarding the $Paco_2$ in these patients. Although subsequent studies by Clark et al,[5] Ogawa et al,[24] and Gerstmann et al[6] have not demonstrated increased adverse outcomes, the HIFO study of 176 infants randomly assigned to HFOV or CV again showed a marginally significant increase in severe grades of IVH.[25] Interestingly, infants treated with HFOV in that study also had significantly lower $Paco_2$ levels compared with infants treated with CV.

A ventilator strategy designed to promote alveolar recruitment and optimize ventilation/perfusion matching has long been advocated by deLemos and others for HFOV.[9,10] Several investigators have documented the need for volume recruitment maneuvers such as a sustained inflation and showed that optimizing lung volume improves oxygenation, reduces lung injury, and improves surfactant function.[7,26–29] The same effect was observed with HFJV in animal models of surfactant deficiency.[30,31]

HFJV has traditionally been used to treat airleak; therefore, the HFJV strategy traditionally used emphasized the ability of HFJV to provide excellent ventilation and adequate oxygenation at relatively low airway pressures.[2,3,32,33] The effectiveness of this approach in the treatment of airleak has been well documented.[1–4] However, the sound physiologic rationale of HF-OPT in homogeneous lung disease, along with unpublished preliminary laboratory and clinical experience with this particular approach to HFJV, led the authors to adopt HF-OPT for the collaborative clinical study of HFJV in uncomplicated RDS. Perhaps because this strategy had not been extensively validated with HFJV in the clinical setting, there was clearly reluctance on the part of some investigators/clinicians to adhere to it. Although this protocol issue detracted somewhat from the primary CV-HFJV comparison, it provided a unique opportunity to compare the relative effectiveness and safety of the two strategies in a homogenous and, in all other respects, comparable population.

It is of note that even as small an increase as 1 cm H_2O in PEEP and $\overline{Paw}$ often appeared to be effective in improving oxygenation substantially. It has been well documented that the benefit of sustained inflation (as reflected in lung volume and oxygenation) is rapidly lost unless the PEEP is maintained above the derecruitment pressure.[26] The presumed mechanism of action with HFJV is that PEEP stabilizes lung volume during the expiratory phase, whereas the background IMV serves to periodically provide the necessary opening pressures to achieve alveolar recruitment. We did not measure lung volume directly in this study; therefore, the effect of ventilator strat-

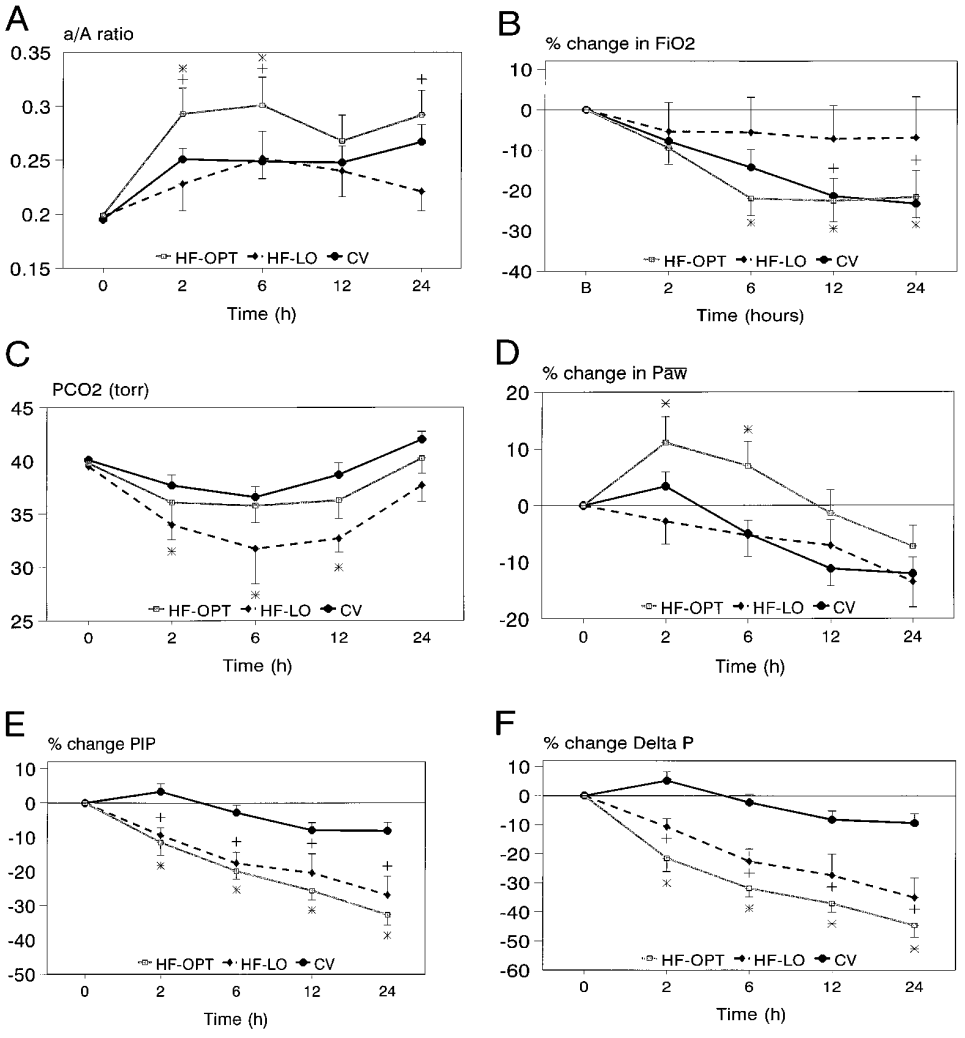

Figure. Changes during the first 24 hours of the study in gas exchange, F_{IO_2}, and airway pressures. F_{IO_2} and airway pressures are shown as percent change from baseline attributable to somewhat different baseline values. All data are expressed as mean ± SEM. Panel A shows arterial/alveolar P_{O_2} ratio. $P < .05$ for HF-OPT versus other two groups; post hoc testing showed †$P < .05$ for HF-OPT versus baseline at 2, 6, and 24 hours and *$P < .05$ for HF-OPT versus other two groups at 2 and 6 hours. Panel B shows F_{IO_2}; HF-LO is different from the other two groups ($P < .01$); HF-OPT is different from baseline and from HF-LO at 6, 12, and 24 hours (*$P < .01$); CV is different from baseline and from HF-LO at 12 and 24 hours (†$P < .01$). Panel C shows P_{aCO_2}; HF-LO is different from the other two groups over the 24-hour period ($P < .05$.). The 2, 6, and 12 time points for HF-LO are different from baseline (*$P < .05$). Panel D shows $\overline{Paw}$; there were no significant intergroup differences overall. The HF-OPT group was significantly above baseline and significantly different from the other two groups at 2 and 6 hours (*$P < .05$). Panel E shows PIP. Both HFJV groups were significantly below baseline at all time points and different from CV (*†$P < .001$). Panel F shows ΔP; both HFJV groups were significantly below baseline at all time points and different from CV (*†$P < .001$).

egy on lung volume can only be inferred from the oxygenation response.

An important element of HF-OPT is the emphasis on separating the control of oxygenation from that of ventilation. When PEEP is maintained at an arbitrary low level, a situation often arises in which hyperventilation is perpetuated inadvertently, because additional reduction of PIP, the standard manner of reducing minute ventilation, is precluded by marginal oxygenation. With HF-OPT, increasing the PEEP, while simultaneously lowering the PIP, allows the user to narrow the ΔP, thereby reducing tidal volume, while maintaining or increasing $\overline{Paw}$. This phenomenon is the likely explanation for the observed differences in P_{aCO_2} between HF-OPT and HF-LO, despite identical target blood gas values.

We conclude that when initiated early in the course of the disease, HFJV reduces the incidence of BPD at 36 weeks' PCA and the need for home supplemental oxygen in premature infants with uncomplicated RDS, but does not reduce the risk of acute airleak. There appears to be no increase in adverse outcomes when compared with CV. HF-OPT improves oxygenation, reduces exposure to hypocarbia, and appears to reduce the incidence of severe grades of IVH and/or PVL. Additional large, well-controlled studies are needed to clarify the role of ventilator type and strategy on pulmonary and neurologic outcomes.

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Multicenter Controlled Clinical Trial of High-frequency Jet Ventilation in Preterm Infants With Uncomplicated Respiratory Distress Syndrome

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