Benefits of High Frequency Oscillatory Ventilation for Premature Infants

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ABSTRACT: **Background:** High frequency oscillatory ventilation based on optimal lung volume strategy is one of the accepted modes of ventilatory support for respiratory distress syndrome in very low birth weight infants. In 1999 it was introduced in our unit as the primary ventilation modality for RDS.

Objectives: To evaluate if the shift to HFOV influenced the outcome of ventilated VLBW infants in the neonatal intensive care unit of Carmel Medical Center.

Methods: Data were obtained from the medical charts of VLBW infants born at Carmel Medical Center, and late mortality data from the Israel Ministry of Internal Affairs records. A retrospective analysis and a comparison with a historical control group ventilated by the conventional method were performed.

Results: A total of 232 VLBW infants with RDS were mechanically ventilated during the period 1995 to 2003: 120 were ventilated using HFOV during 1999–2003 and 102 infants using CV during 1995–1999. The mean gestational age of survivors was 27.4 ± 2 weeks in the HFOV group and 28.4 ± 2 in the conventional ventilation group ($P = 0.03$). The sub-sample of infants with birth weight < 1000 g ventilated with HFOV showed higher survival rates than the infants in the conventional ventilation group, 53 vs. 25 (64.6% vs. 44.6%) respectively ($P < 0.05$). A trend for lower incidence of pulmonary interstitial emphysema was observed in the HFOV group.

Conclusions: The introduction of HFOV based on optimal lung volume strategy proved to be an efficient and safe method of ventilation support for VLBW infants in our unit.

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KEY WORDS: high frequency oscillatory ventilation, conventional ventilation, very low birth weight infants, mortality, morbidity, outcome

Although high frequency oscillatory ventilation is one of the accepted modalities of mechanical ventilation for respiratory distress syndrome in very low birth weight premature infants, its efficacy and safety are still controversial [1-3]. There is disagreement about the advantage of HFOV over conventional ventilation in the treatment of respiratory failure in preterm infants in terms of mortality, chronic lung disease, grade III-IV intraventricular hemorrhage, and periventricular leukomalacia [4-8]. However, the use of HFOV based on the optimal lung volume strategy is supported by many clinicians and has been shown to improve survival without an increase in the incidence of chronic lung disease [2,9-11].

As demonstrated in animal models, HFOV improved lung function and mechanics and reduced inflammatory mediator levels [12]. Those assigned to HFOV, using optimal lung volume strategy, showed early and sustained improvement in pulmonary mechanics and gas exchange [13]. Early and exclusive use of HFOV combined with optimal lung volume strategy had a beneficial effect during the acute phase of lung injury [14] and decreased exogenous surfactant requirements [8].

In our setting (the neonatal intensive care unit, Carmel Medical Center, Haifa, Israel), the strategic decision to use HFOV as a primary ventilation modality in VLBW infants suffering from RDS was made in June 1999. Thus, there were two historical periods of ventilation policy – CV (1995 to June 1999) and HFOV (June 1999 to 2003). Considering the controversial data in the literature, along with our positive subjective experience with HFOV, it was decided to review the data and clarify whether our shift to HFOV had been justified.

PATIENTS AND METHODS

Data on morbidity and mortality were obtained from the medical charts of VLBW infants who were born at Carmel Medical Center during the period 1995 to 2003 and were mechanically ventilated for RDS. A retrospective analysis was performed. In addition, the Israel Ministry of Internal Affairs records of death were used to reveal mortality after discharge from hospital.

Infants in the CV group were ventilated using BP 2001 (Bear, BV 166, InterMed, CA, USA) or SLE 2000 (Specialized

RDS = respiratory distress syndrome
HFOV = high frequency oscillatory ventilation
VLBW = very low birth weight
CV = conventional ventilation

Laboratory Equipment Ltd., UK). Infants in the HFOV group were ventilated using 3100A BSI Oscillatory Ventilator (Sensor Medics, USA) or by SLE 2000. The optimal lung volume strategy was used in the HFOV group. Permissive hypercapnea was accepted during both historical periods with the same goal parameters of ventilation: Sat O_2 92% and higher, pCO_2 around 40–60 mmHg and pH ≥ 7.2. The same type of surfactant (Curosurf, Poractant Alfa, Chiesi Farmaceitici, Parma, Italy) was used for both groups.

Statistical analysis was performed with SPSS software (version 11.5) and SAS software (version 9.1). Demographic data, clinical parameters and categorical outcomes were compared between the CV and HFOV groups using the chi-square test or, when appropriate, Fisher's exact test. Continuous variables were compared by means of the *t*-test or Mann-Whitney non-parametric test, as appropriate. Survival curves were estimated by the Kaplan-Meyer method and compared by a log-rank test. Multivariate regression models (logistic model and Cox proportional hazard model) were applied to adjust group comparisons to possible confounders with regard to morbidity and survival data. The model included gestational age and birth weight as covariates, and group and any steroid treatment as factors. An infant served as the main observational unit for the analysis. When mothers' demographic data were analyzed, a mother was used as an additional observational unit. In addition, in order to take account of the possible correlation among twins and triplets, mixed models were also applied. However, since the results of these models appeared to be similar to the results obtained by the simple approach, only the latter are presented in this paper. *P* values less than 0.05 were considered significant.

RESULTS

This retrospective analysis included 232 VLBW infants who were born at Carmel Medical Center during the period 1995 to 2003 and required mechanical ventilation for the treatment of RDS. Of these infants, 102 were born during the period January 1995 to June 1999 and were ventilated by intermittent mandatory ventilation/synchronized intermittent mandatory ventilation (CV group) as a primary ventilation modality, while 130 infants born between June 1999 and December 2003 were primarily ventilated by HFOV.

There were no significant demographic differences between the groups. Maternal obstetric history, pregnancy follow-up and mode of delivery were similar. The frequency of twins in the HFOV group was twice that in the CV group, 22 (20.6%) vs. 11 (13.1%) ($P < 0.05$) and there were no triplets, while in the CV group there were four sets of triplets.

The infants' characteristics are showed in Table 1. Infants in the HFOV group tended to have lower birth weight and lower gestational age, but the differences were not statistically significant. A larger number of infants in the HFOV group received two doses of prenatal bethametasone (Celestone®): 79 (60.7%) vs. 51 (50%) in the CV group ($P = 0.008$). Partial (one dose) prenatal steroid treatment did not yield significant differences between the two groups.

Table 1. Infants' characteristics and morbidity

	CV (n=102)	HFOV (n=130)	*P*
Males	51 (50.0%)	62 (47.7%)	NS
Females	51 (50.0%)	68 (52.3%)	NS
Mean gestational age ± SD (wks)	27.4 ± 2.5	26.9 ± 2.4	NS
Mean birth weight ± SD (g)	952 ± 253	903 ± 252	NS
Birth weight < 1000 g	56 (54.9%)	82 (63.1%)	0.15
Prenatal bethametasone Two doses One dose	 51 (50.0%) 23 (22.5%)	 79 (60.7%) 37 (28.5%)	 0.005 0.05
Pneumothorax	19 (18.6%)	18 (13.8%)	
Pulmonary interstitial emphysema	12 (11.8%)	7 (5.4%)	0.08 in univariate analysis, 0.07 in multivariate analysis
Pneumopericardium	3 (2.9%)	1 (0.8%)	NS
Patent ductus arteriosus	28 (27.5%)	28 (21.5%)	NS
Indomethacin treatment for PDA	22 (21.6%)	20 (15.4%)	NS
Surgical ligation of PDA	1 (1.0%)	10 (7.7%)	< 0.05 in univariate, 0.09 in multivariate analysis
Necrotizing enterocolitis	19 (18.6%)	20 (15.4%)	NS
Laparotomy for NEC	8 (7.9%)	10 (7.7%)	NS
IVH Grade 3-4/ examined	10/80 (12.5%)	24/122 (19.7%)	NS
PVL/examined	8/43 (18.6%)	10/83 (12.0%)	NS
IVH and/or PVL/examined	11/41 (26.8%)	18/82 (22.0%)	NS
ROP more than grade 2/ examined infants	14 (28.6%)/49	39 (39.0%)/100	NS
Cryo/laser treatment for ROP	8/49 (16.3%)	32/100 (32%)	< 0.05 in univariate analysis, 0.07 in multivariate analysis
Oxygen at 28 days/ survived at 28 days	44/80 (55.0%)	65/104 (62.5%)	NS
Oxygen at 36 weeks GA/survived at 36 weeks GA	26/74 (35.1%)	40/100 (40%)	NS
Systemic steroids/ total	17/102 (16.9%)	10/130 (8.1%)	< 0.05
Median mechanical ventilation days, for discharged infants (range)	5.5 (1–190)	6.5 (1–104)	NS
O_2 supplementation days in discharged infants Mean ± SD Median (range)	 46 (± 47) 23 (1–232)	 45 (± 44) 45 (2–176)	 0.10
Discharge with oxygen/survived by discharge day	11/65 (16.9%)	26/97 (26.8%)	NS

NEC = necrotizing enterocolitis, IVH = intraventricular hemorrhage, PVL = periventricular leukomalcia, ROP = retinopathy of prematurity, GA = gestational age

MORBIDITY

As shown in Table 1, there were no statistically significant differences in most morbidity parameters between the two groups. Univariate analyses demonstrated a higher frequency of surgical ligation of patent ductus arteriosus in the HFOV group compared to the CV group (7.7% vs. 1%, $P < 0.05$). After adjustment for birth weight, gestational age and betamethasone treatment it was no longer significant ($P = 0.09$). However, a trend for lower incidence of pulmonary interstitial emphysema was observed in the HFOV group (5.4% vs. 11.8%, $P = 0.08$ and $P = 0.07$, in the univariate and multivariate models, respectively).

Treatment for retinopathy of prematurity (cryotherapy or laser) tended to be more frequent in the HFOV group than in the CV group (32% vs. 16.3%, $P < 0.05$ and $P = 0.07$, in the univariate and multivariate models, respectively).

Although more infants from the CV group were treated by systemic steroids – 17/102 (16.9%) vs.10/130 (8.1%) in the HFOV group ($P < 0.05$) – there were no significant differences between the groups in oxygen supplementation at 28 days and 36 weeks gestational age [Table 1]. Of the 232 study infants, 162 were discharged from the hospital: 97 (74.6%) in the HFOV group and 65 (63.7%) in the CV group. The median duration of mechanical ventilation for the discharged babies and the number of infants who were discharged home with supplemental oxygen are shown in Table 1.

During the hospitalization, based on clinical judgment, 6 babies in the CV group (5.8%) were switched to HFOV, and 43 babies in the HFOV group (33.8%) were ventilated later using CV; most of them needed ventilation for surgical procedures or during sepsis after resolution of the RDS.

Figure 1. [A] Kaplan-Meier overall survival curves. In both sub-samples of body weight, ‹ 1000 g and ≥ 1000 g, no differences are demonstrated between the ventilation groups in the incidence of both early neonatal deaths and neonatal deaths. The differences appeared after the 30th day of an infant's life, with higher although not statistically significant survival rates in the HFOV group.
[B] Kaplan-Meier survival curves for infants with BW ‹ 1000 g. After the 30th day of an infant's life, higher and statistically significant survival rates are demonstrated in the HFOV group.

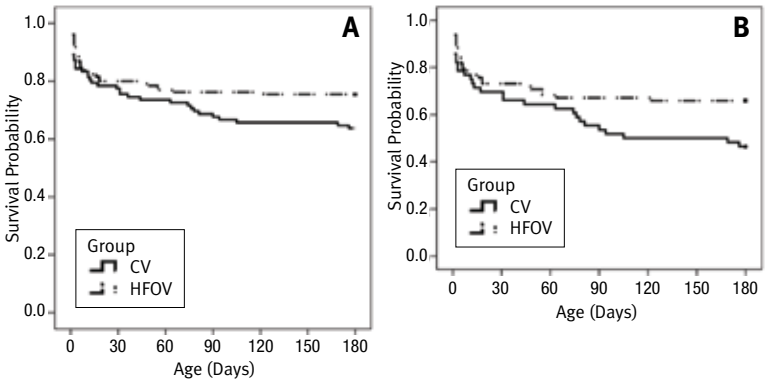

Table 2. Causes of death before discharge

	CV (n=36/102)	HFOV (n=32/130)
Respiratory failure	3	4
Severe cystic chronic lung disease	5	
Pulmonary hemorrhage		2
Pleuropulmonary fistula, pneumothorax	1	
Pneumopericardium	2	
Hypoplastic lungs	2	
Cytomegaloviral pneumonitis	3	
Massive myocardial infarction	1	
Cardiac arrest at intubation for elective surgery		1
Hypovolemic hemorrhagic shock	1	
Septic shock	3	4
Acute renal failure	5	2
Renal tubular dysplasia, anuria		1
Extreme immaturity	8	10
IVH grade IV	1	5
NEC	1	2
Hepatic cirrhosis		1

SURVIVAL ANALYSIS

The median follow-up for survival was 2.6 years overall: 2.1 years and 6.1 years for the HFOV and CV groups respectively. Of the 232 infants, 68 babies died: 34 (50%) before 7 days of life (early neonatal deaths) and an overall of 66 infants (97%) during the first year of life. Two more babies died after 1 year of age. Table 2 demonstrates the causes of the infants' death before discharge. There are no data for causes of death after discharge. The mean gestational age of the survivors was significantly lower in the HFOV group (27.4 ± 2 weeks) than in the CV group (28.4 ± 2 weeks, $P = 0.03$).

The Kaplan-Meier survival curves are presented in Figure 1. Overall survival was higher in the HFOV group: 97 (74.6%) vs. 62 (60.8%) ($P < 0.05$). As can be seen from the survival curves, there were no differences between the two groups in the incidence of both early neonatal deaths (16.2% vs. 16.7) and neonatal deaths (20% vs. 21.5%) in the HFOV and CV groups, respectively. However, the differences appeared after the 30th day of life [Figure 1A]. The HFOV group demonstrated higher survival rates in both sub-samples of birth weight: < 1000 g and ≥ 1000 g. This finding was statistically significant only for the sub-sample of the smaller infants. As seen in Figure 1B, of all the infants with birth weight under 1000 g, 53 infants (64.6%) in the HFOV group survived, compared to only 25 (44.6%) in the CV group ($P < 0.05$). For infants with the higher birth weight (> 1000 g), 44 (91.7%) in the HFOV group survived vs. 37 (80.4%) in the CV group ($P = 0.15$).

Table 3. Multivariate Cox regression model for survival

			95.0% CI for hr	
Predictors for survival	***P***	**Hazard ratio (hr)**	**Lower**	**Upper**
Ventilation method (HFOV vs. CV)	0.034	0.592	0.364	0.962
Birth weight (g)	0.002	0.997	0.996	0.999
Gestational age (wks)	0.060	0.850	0.717	1.007
Prenatal steroids (yes vs. no)	0.037	0.563	0.328	0.966

The Cox regression model was applied to assess the influence of other parameters on survival and to adjust the comparison data between the groups to possible confounders. The following parameters were evaluated: mother's ethnicity and education, prenatal steroids, the ventilation mode, and infant's gender, gestational age and birth weight. In the univariate analysis, low gestational age, low birth weight and no prenatal steroids were associated with increased death risk, while gender, ethnicity and mother's education were not found to be statistically significant. Table 3 presents the results of a multivariate Cox model including significant predictors for survival from univariate analysis. It can be seen that the most significant predictor was birth weight. After controlling these variables, the ventilation mode was found to be significant (the hazard rate for HFOV mode relative to conventional ventilation was 0.59; 95% confidence interval 0.36–0.96), meaning that the chance to survive was higher in infants ventilated by HFOV. In addition, among the infants who survived, the mean birth weight was significantly lower in the HFOV group (964 ± 239 vs. 1048 ± 232, $P < 0.05$).

DISCUSSION

The outcome of VLBW premature infants managed by different ventilation modalities is controversial. In our retrospective analysis the infant population resembled the infants enrolled in published studies in terms of their birth weight and gestational age [2,4,5,9,10,14]. The two groups, treated with two different ventilation modalities, were not significantly different in maternal demographic data or in medical history. The incidence of twins and triplets was different between the two groups – with a prevalence of twins in the HFOV group and triplets in the CV group. The mode of delivery was similar in both groups. There were no significant differences between the two groups concerning partial (one dose) prenatal steroid treatment; however, there were more cases of prenatal full betamethasone administration (two doses) in the HFOV group and it was statistically significant.

Most previous studies did not demonstrate significant differences in survival between the groups of infants ventilated by different ventilation modalities. Data presented by Courtney et al. [10] were different and showed that 56% of infants assigned to HFOV survived without a need for supplemental oxygen at 36 weeks postmenstrual age, compared to 47% of those receiving CV ($P = 0.046$). In a study conducted by Johnson and co-authors [2], the composite primary outcome (death or chronic lung disease, diagnosed at 36 weeks gestational age) was not statistically different in the two groups of ventilation modalities (HFOV 66% and CV 68%). Meta-analysis of the eligible studies comparing the two methods undertaken by the Cochrane Database revealed no evidence of effect of ventilation mode on mortality at age 28–30 days [6]. According to our data, the survival rate of infants from the HFOV group was significantly higher, when adjusted for gestational age, birth weight and prenatal steroids. Considering that the administration of antenatal corticosteroids had been associated with an overall reduction in neonatal death [15], we performed multifactorial analysis. After prenatal steroids administration had been taken as one of the factors for adjustment, survival of infants from the HFOV group was still significantly higher. A significantly higher survival rate was observed for babies with < 1000 g birth weight, but it was not observed for those weighing ≥ 1000 g. Extremely low birth weight premature infants constitute the most challenging population for respiratory management and chronic lung injury prevention. Our study suggests that HFOV based on optimal lung volume strategy is beneficial for the survival of extremely low birth weight infants.

According to our data, most of the morbidity parameters were similar in both groups. However, in our population, the trend for decreased occurrence of pulmonary interstitial emphysema in the HFOV group was revealed. Yet, published data considering the incidence of air-leak syndrome in VLBW infants ventilated by different modalities remain contradictory [2,6,16,17].

Previous publications on the incidence of chronic lung disease is also controversial [2,5,8,9,14,17]. However, a prospective randomized comparison of HFOV and CV in RDS undertaken by Clark et al. [4] demonstrated a higher incidence of chronic lung disease in the CV group of VLBW infants. In a randomized, multicenter clinical trial, VLBW infants who were assigned to HFOV were successfully extubated earlier than infants assigned to conventional ventilation ($P < 0.001$) [10]. A meta-analysis undertaken by Henderson-Smart and team [6] suggests a small reduction in the rate of chronic lung disease with HFOV use, but the evidence is weakened by the inconsistency of this effect across trials and the overall borderline significance. In addition, HFOV was associated with a significant reduction in the aggregated outcome (death or chronic lung disease at term gestation), but this effect was not consistent across other studies [2,16].

Since a number of publications had reported causal relationships between prolonged early systemic steroid treatment of VLBW infants and cerebral palsy development [18,19],

postnatal steroids began to be used with more caution. In spite of a different systemic steroid administration policy for chronic lung disease in the two groups of our study, there was no significant difference in disease incidence between the two groups. There were no statistically significant differences in oxygen supplementation – either at 28 days of age or at 36 weeks corrected gestational age.

Previous publications have not reported any differences in the incidence of PDA, necrotizing enterocolitis and ROP between the groups ventilated by HFOV and CV [9,10]. The incidence of PDA and necrotizing enterocolitis was similar in both groups of our cohort as well. The only difference found was that more patients were surgically treated for PDA in the HFOV group, but when adjusted for birth weight, gestational age and betamethasone treatment, it was not statistically significant. Although no significant differences were found between the two groups regarding the incidence of ROP, diode laser therapy was more frequently used in the HFOV group. The increased number of patients treated by laser since 1999 could be explained by the changes in treatment approach to ROP during recent years. It has been recommended that the disease be treated at earlier stages, namely, to start treatment at the stage of pre-threshold disease and not at the stage of threshold disease as previously accepted [20].

The fact that after RDS had been resolved more surgical interventions for PDA and ROP were indicated in the HFOV group helps to explain the need to reventilatie the HFOV group babies using CV.

After controlling for birth weight, gestational age and prenatal steroids, no significant differences were found between the two groups regarding the incidence of brain injury manifestations, either in intraventricular hemorrhage grade III-IV or in periventricular leukomalacia. Considering the early publications presenting controversial data on brain injury in VLBW ventilated by HFOV, this finding is especially important. Some trials using different HFOV techniques without the establishment of optimal lung volumes reported a higher rate of brain damage and air leaks (grade III-IV intraventricular hemorrhage or cystic periventricular leukomalacia) [1,2,6-8,13,17]. On the other hand, previous studies on HFOV based on the use of initial alveolar recruitment maneuvers and the use of optimal lung volume strategy did not yield such results [2,5].

Some limitations in our study need to be considered. First, the analysis was retrospective, based on data taken from medical records of different historical periods, although the policy of permissive hypercapnea and the same type of surfactant were used during the study period. Second, while more infants in the HFOV group received antenatal steroids, the influence of antenatal steroids administration on survival was neutralized after multifactorial analysis. Third, several infants in both groups, as mentioned before, were switched to another ventilation modality. Six babies initially ventilated with the conventional method were switched to HFOV because CV was not effective. Likewise, 43 babies who had been initially ventilated by HFOV were ventilated later using the conventional method, mainly for anesthesia given during surgical procedures or for septic episodes. A number of infants did not show a good response while initially ventilated by HFOV and they were switched to CV. Based on "intention to treat," the babies were assigned to the appropriate group taking in account the ventilation modality (HFOV or CV) used for primary management of RDS .

PFA = patent ductus arteriosus
ROP = retinopathy of prematurity

CONCLUSIONS

Our data demonstrate that the survival of HFOV-ventilated infants was significantly higher in a subpopulation of premature babies with lower birth weight, despite having more risk factors for death. We also found that HFOV may be as efficient and safe a primary method of mechanical ventilation for small premature infants as conventional ventilation has proven to be. Although the analysis was retrospective, it showed that HFOV based on the optimal lung volume strategy was beneficial for the treatment of VLBW infants, and especially extremely low birth weight infants, without increasing their morbidity. In our department, the decision to ventilate VLBW babies with RDS using HFOV was legitimated.

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