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A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome

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Abstract *Objective*: To compare the effectiveness and safety of very early high-frequency oscillatory ventilation (HFOV) with conventional mechanical ventilation (CMV) in treatment of the respiratory distress syndrome (RDS) and to evaluate their impact on the incidence of chronic pulmonary disease and early and late morbidity of very low-birthweight neonates.
Design: A prospective randomized clinical trial.
Setting: Tertiary neonatal intensive care unit in the Perinatology Center in Prague.
Patients: 43 premature newborns, delivered in the Department of Obstetrics in the Perinatology Center, were randomly divided into two groups (HFOV and CMV) immediately after delivery; 2 patients in each group died, 2 fulfilled crossover criteria from CMV to HFOV, and 2 were excluded because of congenital malformations. Nineteen patients treated with HFOV were therefore compared with 18 infants in the CMV group.
Methods: The two contrasting modes of ventilation were introduced immediately after intubation. Maintenance of optimal lung volume in HFOV to optimize oxygenation and the therapeutic administration of surfactant after fulfilling defined criteria are important points of the strategy and design of the study.
Measurements and main results: Except for a higher proportion of males in the HFOV group ($p < 0.02$), the basic clinical characteristics (gestational age, birthweight, Apgar score at 5 min, umbilical arterial pH), the two groups were similar. In the acute stage of RDS, infants treated with HFOV had higher proximal airway distending pressure with HFOV for 6 h after delivery ($p < 0.05$). For a period of 12 h after delivery lower values for the alveolar-arterial oxygen difference ($p < 0.03$) were noted. The number of patients who did not require surfactant treatment was higher in the HFOV group (11 vs 1, $p < 0.001$). In the HFOV group the authors found a lower roentgenographic score at 30 days of age ($p < 0.03$) and a lower clinical score in the 36th postconceptional week ($p < 0.05$), using these two scoring systems for assessing chronic lung disease according to Toce scale. The incidence of pneumothorax, pulmonary interstitial emphysema, intraventricular hemorrhage and retinopathy of prematurity in both groups was the same.
Conclusions: HFOV, when applied early and when the clinical strategy of maintenance of optimal lung volume is used, improves oxygenation

in the acute stage of RDS, reduces the need of surfactant administration, and can decrease the injury to lung tissue even in extremely immature newborns to whom surfactant is administered therapeutically.

Key words Extreme prematurity · Oxygenation · Surfactant · High frequency oscillatory ventilation · Chronic lung disease

Introduction

At the present time new methods are being explored to reduce not only the mortality but also the morbidity of very low-birthweight newborns. High frequency oscillatory ventilation (HFOV), which uses tidal volumes lower than dead space, seems to be promising from this standpoint and has been studied since the early 1980s. In 1989 the Multicenter HIFI Group [1], comparing of HFOV and conventional mechanical ventilation (CMV), did not confirm any benefit of HFOV and reported a higher incidence of intraventricular hemorrhage (IVH) and other complications in the HFOV group. These results may not present a valid argument against the administration of HFOV now because there were some methodological weaknesses. The late application of HFOV and the apparent use of a low volume strategy in the HFOV group are crucial flaws in the methodology of the study. Subsequently, during the 1990s there have been several clinical trials which have documented the benefits of HFOV in the following cases: (1) rescue therapy of acute lung failure in newborns and children [2, 3], (2) combination of nitric oxide inhalation and HFOV administration in the treatment of pulmonary hypertension of newborns [4], (3) pre-extracorporeal membrane oxygenation mode of artificial ventilation [5, 6], (4) treatment of respiratory distress syndrome (RDS) and effect on occurrence of acute and chronic complications of prematurity [7–9].

Despite these encouraging results, the benefits of HFOV reported in clinical studies were not as dramatic as those in animal models of RDS. We believe that the reason for this difference is the relatively late use of HFOV in the clinical studies, unlike the animal studies where HFOV was applied immediately after intubation.

The objective of our prospective randomized study was to compare the effectiveness and safety of early HFOV and CMV in very immature infants with RDS and to evaluate their impact on the incidence of chronic pulmonary disease, as well as early and late morbidity.

Materials and methods

From October 1995 to May 1997, very low birth-weight newborns (birthweight 500–1499 g), with estimated gestational age less than 31 completed weeks who might require mechanical ventilation for respiratory insufficiency, were eligible to be entered into the randomized study, provided they were not small for gestational age, had no major congenital anomalies or neuromuscular condition affecting respiration, and were not ventilated because of central nervous system (CNS) or circulatory failure. In that period, 76 very low-birthweight infants were born , among them 46 with a birthweight below 1000 g, in the Perinatology Center of Prague. This is the level III maternity and newborn center for Prague and Central Bohemia. Of the 76 eligible infants, 33 had to be excluded. Twenty-four infants with mild or moderate clinical sings of RDS after initial stabilization in the delivery room (stimulation, inhalation of oxygen, or lung inflation by brief bagging) were supported by nasal continuous positive airway pressure (CPAP) and given surfactant within 2 h, as they required a fractional inspired oxygen (FIO_2) of > 0.30. Nine infants needed only a short inhalation of oxygen after delivery. This left 43 infants, who were entered into the study and randomized into the two treatment groups.

Approval to conduct the trial was given by the Ethical Committee of the First Medical Faculty, Charles University. Eligible newborns were selectively intubated in the delivery room, if good oxygenation could not be achieved despite repeated bagging and/or oxygen administration with early development of respiratory distress and grunting. The intubated patients were randomly assigned to receive either HFOV or CMV using sealed envelopes with treatment assignment based on a table of random numbers. The infants were moved to the neonatal intensive care unit (NICU) immediately to start one of the two modes of artificial ventilation. The NICU is located next to the delivery room so that the period of bagging was minimized. Rapid initiation of ventilation within 20 min postpartum was a key aspect of the study design. After initial respiratory stabilization, performed by adjusting the ventilatory parameters to achieve good oxygenation according to defined strategies, the first dose of surfactant was administered if the criteria for surfactant administration were fulfilled. Then the umbilical or radial artery was cannulated to measure systemic blood pressure and obtain arterial blood samples. A chest radiograph was obtained to confirm the position of the endotracheal tube and arterial catheter and to assess lung volume and the extent of lung disease. These procedures, including the initial blood gas determination, had to be completed within 3 h of delivery.

HFOV (SensorMedics 3100 A)

The oscillation frequency for HFOV was set at 15 Hz and the inspiratory-to-expiratory time ratio was maintained at 0.33 in all infants throughout the study. The pressure amplitude (DP) was adjusted to achieve adequate vibration of the thorax. The proximal airway distending pressure (PA_wDP) was increased step by step to reach optimum lung inflation and alveolar recruitment and to optimize oxygenation as soon as possible. DP was adjusted to the lowest value consistent with normocapnia. PA_wDP was adjusted as lung compliance changed using chest X-rays for guidance with a goal of the right diaphragm at the 9th rib in the midclavicular line. Once adequate lung inflation was achieved and oxygenation was optimized, the FiO_2 was weaned to keep normoxemia (PaO_2 55–80 mmHg).

The patients were weaned to nasal CPAP (nCPAP) when the following criteria were fulfilled: (1) $PA_wDP \leq 6.5\ cm_2O$ and $FIO_2 \leq 0.30$ and (2) the patient started to breathe spontaneously and good breath sounds could be heard during spontaneous breathing.

Crossover criteria from HFOV to CMV

Despite optimum lung inflation (confirmed by X-rays) and arterial normotension, adequate blood gases could not be achieved (PaO_2 > 50 mmHg and/or CO_2 < 65 mmHg).

CMV (Bear-Cub 2100, Infant star)

Time-cycled, pressure-limited conventional ventilators with or without synchronization were used. An initial ventilator rate of 30–60 breaths per min and an inspiratory time of 0.3–0.5 s were used. The positive end-expiratory pressure (PEEP) was in the range of 3–5 cm_2O. The peak inspiratory pressure (PIP) was adjusted to obtain an adequate chest rise. Oxygenation was increased primarily by adjusting MA_wP when FIO_2 was > 0.6 and by adjusting FIO_2 when FIO_2 was < 0.40. CO_2 elimination was controlled by increasing minute ventilation by adjusting DP or frequency depending on the need for MA_wP. The frequency was decreased slowly and carefully to maintain normocapnia and avoid labored breathing.

The ventilation parameters were adjusted as indicated by blood gases, weaning inspiratory pressure or rate in response to improving $PaCO_2$ and FIO_2 or MA_wP in response to improving PaO_2. When spontaneous breathing activity with the following ventilator settings was reached ($MA_wP \leq 5$ cm_2O, $FIO_2 \leq 0.30$), the frequency of intermittent mandatory ventilation was decreased below 15 permin and extubation to CPAP was attempted within a few hours. If a CPAP > 7 cm_2O and an $FIO_2 > 0.40$ were needed, reintubation was considered.

Crossover criteria from CMV to HFOV

HFOV was indicated if the following ventilation parameters were reached to maintain PaO_2 > 50 mmHg or $PaCO_2$ < 65 mmHg with a pH > 7.20: $MA_wP \geq 15$ cm_2O, PIP ≥ 35 cm_2O with $FIO_2 \geq 0.80$.

Surfactant administration

Alveofact suspension 1.2 ml/50 mg (Boerhinger Ingelheim) was used. The dosage of the surfactant was 50 mg/kg for one dose. The first dose of surfactant was always administered within 3 h of intubation if a homogeneous lung disease such as RDS due to surfactant deficiency was present and if the ventilator parameters initial respiratory stabilization did not reach the following values within the 3 h period after delivery: (1) in HFOV: $FIO_2 \leq 0.35$ or $PA_wDP < 12$ cm_2O in newborns weighing ≥ 1000 g and $PA_wDP \leq 10$ cm_2O in newborns weighing < 1000 g and (2) in CMV: FIO_2 was less than 0.35.

Subsequent doses (up to four) of surfactant were administered in the HFOV group if the PA_wDP had increased by at least 15 % above the lowest value reached after the previous administration of surfactant, and in both groups if the FIO_2 had not decreased below 0.35 % or had increased more than 15 % from the original value after the previous administration.

Prenatal induction of pulmonary maturation

Dexamethasone was given parenterally to mothers with signs of premature labor or with premature rupture of membranes at ≤ 32 weeks of gestation. Prenatal steroid use was judged to have been completed if 3 doses of 12 mg dexamethasone were administered to mothers before delivery. Since July 1996, thyroid releasing hormone (TRH) has been used with dexamethasone. The induction of pulmonary maturation was considered complete after the administration of 4 times 400 μg of TRH.

Postnatal steroid use

When the oxygen requirement increased ($FIO_2 \geq 0.35$) and the pulmonary X-ray picture confirmed dysplastic changes without clinical and laboratory signs of infection in patients older than 10 days, dexamethasone treatment was started with a dose of 0.4 mg/kg per day divided into two doses and continued in decreasing dosage for 10 days. In some patients this treatment was repeated during the hospitalization period.

Arterial blood samples were taken as needed in the acute phase of RDS. PA_wDP in the HFOV group , MA_wP in the CMV group, oxygenation index, alveolar-arterial oxygen difference ($A–aDO_2$), PaO_2/ FIO_2 ratio, and $PaCO_2$ were determined during the first 80 h starting with the initial blood gas taken within 3 h of initial stabilization.

Hemodynamically significant persistent ductus arteriosus (PDA) was diagnosed from the clinical signs and confirmed by means of complete echocardiographic examination. The h.s. PDA was treated by intravenous indomethacin (Indocin, Merck Sharp & Dohme). The occurrence of acute ventilator complications, such as pneumothorax and pulmonary interstitial emphysema,

Table 1 Demographic data (*CHD* congenital heart disease, *TRH* thyroid releasing hormone)

	HFOV group	CMV group
No. of randomized patients	22	21
No. of excluded patients (reason)	1 (CNS[a])	1 (CHD)
No. of patients who died/mortality rate	2/21 (9.5 %)	2/20 (10 %)
No. of patients crossed over	0	2
No. of patients evaluated	19	18
Gestational age (completed weeks) (mean ± SD)	26 ± 1.8	26 ± 1.6
Birthweight (g) (mean ± SD)	824 ± 177	851 ± 189
Male gender	78.9 % (15/19)*	44.4 % (8/18)
Apgar score (5 min) (median, 95 % confidence limits)	7 (5, 9)	7 (6, 9)
Umbilical cord artery pH (mean ± SD)	7.24 ± 0.09	7.25 ± 0.08
Prenatal steroid use	52.6 % (10/19)	50 % (9/18)
Prenatal TRH use	21 % (4/19)	16.6 % (3/18)

* $p < 0.02$

[a] CNS pathology, meningitis

were evaluated by chest radiographs. Craniosonography was performed in all patients on days 1, 3, and 10 of life to assess the occurrence of IVH. The Papile classification for the grading of IVH was used [10]. The Toce scale [11], a clinical and roentgenographic scoring system, was used for the evaluation of chronic lung disease on the 30th day of life and in the 30th and 36th week postconception. The maximum clinical score for the most severely affected newborns was 15, and the range of scores for a given chest roentgenograph, from 0 to 10. Roentgenographic score was assessed by a radiolologist unaware of treatment group. Retinopathy of prematurity (ROP) was classified according to the international ROP classification from 1987 [12].

Statistical analysis

Data were tested for normal and nonnormal distribution. Normally distributed data are given as mean ± SD, nonnormal data as median and confidence limits. Normally distributed variables (airway pressures, blood gases) were tested by analysis of variance. Nonnormal data (oxygen use, duration of artificial ventilation) were analyzed by the Wilcoxon rank sum test.

The roentgenographic and clinical scores according to the Toce classification are calculated from separate categorical variables to reach a final value. Categorical variables were tested by Fisher's exact test. A p value of < 0.05 was considered statistically significant for all tests.

Results

Demographic data on the patients are given in Table 1. From September 1995 to April 1997, 43 patients, who met the entry criteria, were randomized for treatment. Of these, 4 patients died, 2 were excluded, and 2 in the CMV group fulfilled crossover criteria from CMV to HFOV. The two crossedover patients were successfully treated with HFOV and survived. They were evaluated in the original CMV group (intent-to-treat analysis). The mortality was similar in these two groups (HFOV 2/21, 9.5 % vs control 2/20,10 %). In June 1997, 37 newborns were available for final analysis; 18 in the CMV group and 19 in the HFOV group. Gestational age, birthweight, Apgar scores at 5 min, and umbilical artery pH were similar in the two groups. In the HFOV group, despite random allocation, there were significantly more males than females ($p < 0.02$). Prenatal steroids and TRH administration to accelerate pulmonary maturation were not significantly different. The severity of RDS and the incidence of PDA requiring treatment with indomethacin were also similar in the two groups.

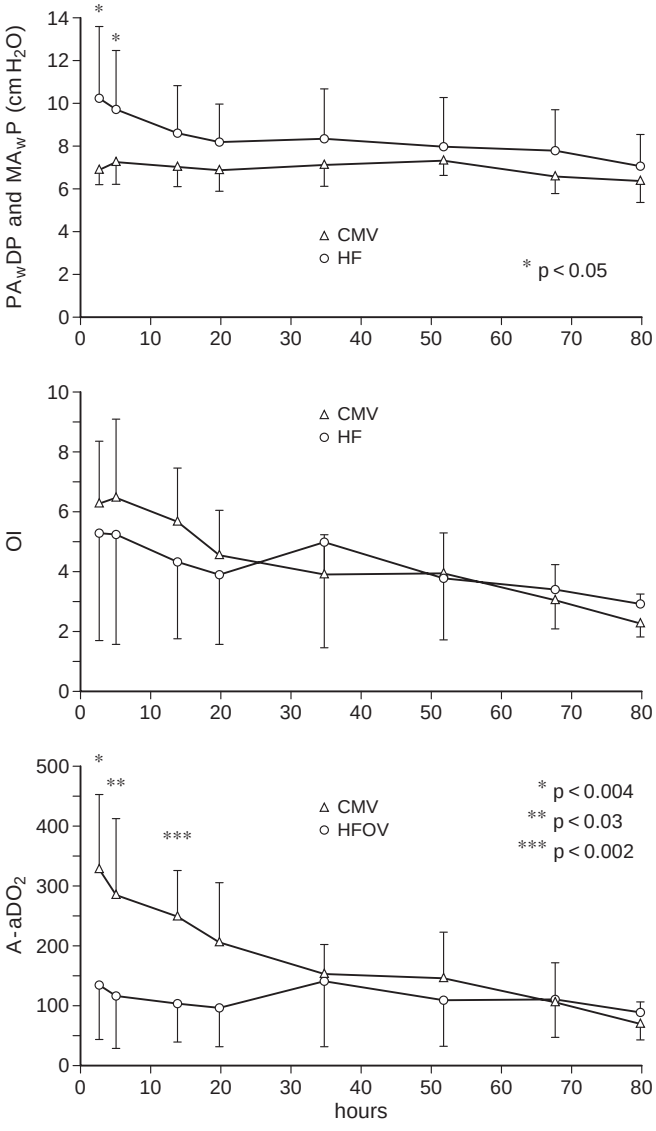

Fig. 1 Comparison of PA_wDP and MA_wP *top panel*, oxygen index *OI middle panel* and A-aDO_2 *bottom panel* between HFOV and CMV for 80 h after the first arterial blood gas determination. Values are mean ± SD. On the *top panel*, PA_wDP in HFOV (cmH_2O) is higher than MA_wP in CMV. The differences were statistically significant only during the initial 6 h ($p < 0.05$). The OI was very similar in both groups over the 80 h *middle panel*. The *bottom panel* illustrates the lower A-aDO_2 in HFOV treated neonates during the 12 h ($p < 0.03$). After initial ventilatory stabilization, A-aDO_2 remained at very similar low values in the HFOV group during the following 80 h

Acute phase of RDS

The evaluation of the acute phase of RDS treated by two different modes of ventilation is illustrated in Figs. 1 and 2. Figure 1 shows the MA_wP in CMV is lower than the PA_wDP in HFOV in the first 6 h after delivery ($p < 0.05$). In the subsequent 74 h, the PA_wDP was still 1–2 cm H_2O higher in the HFOV group but no longer significantly different. Lower values of A-aDO_2 were found in the HFOV group in the 12 h after mechanical ventilation was started in comparison with the CMV group ($p < 0.03$, Fig. 1, bottom panel); however oxygen-

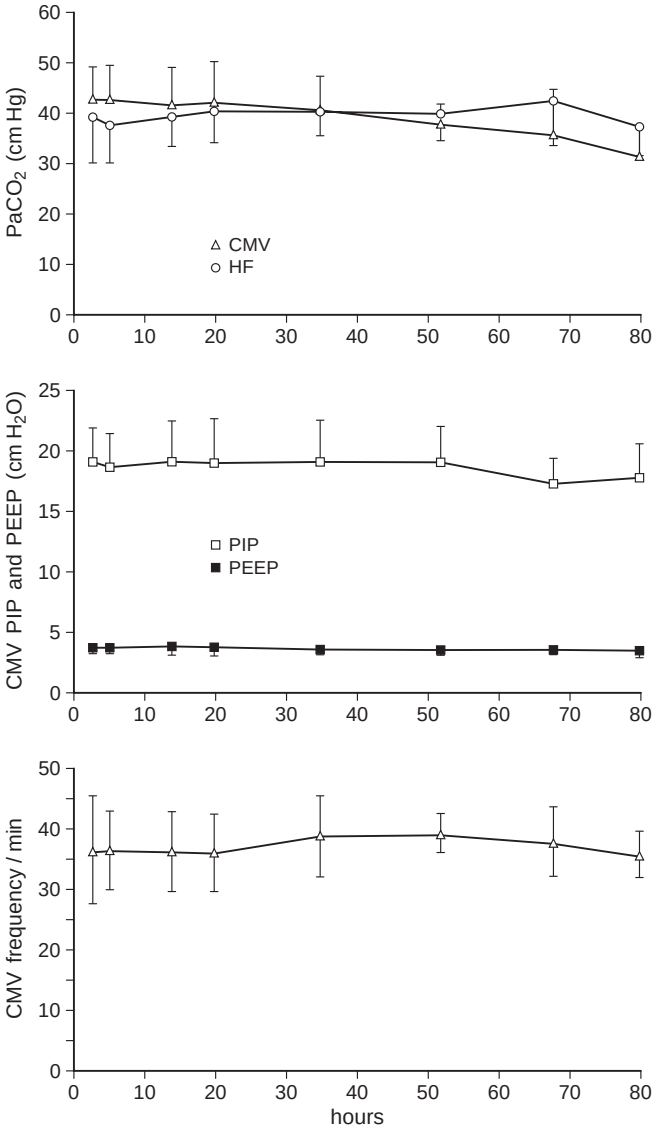

Fig. 2 Comparison of $PaCO_2$ *top panel* between HFOV and CMV for 80 h after the first arterial blood gas determination. The *top panel* shows no differences in $PaCO_2$ values between these two groups. PIP, PEEP *middle panel,* and ventilatory frequency *bottom panel* in CMV over 80 h after the first arterial blood gas determination are shown. These levels were relatively constant during the 80 h. PEEP did not fall below 4 cm_2O

ation index did not differ between the two groups (Fig. 1, middle panel). $PaCO_2$ remained in the range of normocapnia over 80 h after delivery in both groups (Fig. 2, top panel). PIP, PEEP, and ventilatory frequency in the CMV infants are shown in the middle and bottom panels of Fig. 2.

Surfactant dosing and postnatal steroid use

Significantly more patients in the HFOV group did not require any surfactant when compared to the CMV group (11/19 vs 1/18, $p < 0.0001$, Table 2). The number of surfactant doses in all patients was also different between the two groups ($p < 0.0001$). When only patients who received surfactant treatment were compared (8 HFOV and 17 CMV), there were no statistically significant differences in the number of doses between the HFOV and CMV groups (1.5, range 1–3 vs 2, range 1–4). A lower cumulative dose of steroids was found in the HFOV group but this was not significantly different from the CMV group (1.6 mg/kg, range 0–11.3 vs 2.75 mg/kg, range 0–17.5).

Pulmonary outcome (Table 3)

A lower roentgenographic score was found at the age of 30 days in the HFOV group (1, range 0–3 vs 3, range 1–4, $p < 0.03$), but there were no differences in the clinical scores between the two groups. Later, in the 36th postconceptional week, the clinical score was lower (0 vs 2) and more patients had a clinical score of 0 in the HFOV group ($p < 0.05$). The assessment of the roentgenographic score at 36 weeks was abandoned because of ethical considerations, because most of the patients had no clinical signs of chronic lung disease at that time (78.9 % in HFOV patients vs 44.4 % in CMV patients, $p < 0.05$). There were no differences between these two groups in the incidence of airleaks and the duration of mechanical ventilation. Oxygen use tended to be shorter in the HFOV group (20 days, range 1–86 vs 29 days, range 4–107) but the difference was not statistically significant. Fourteen of 19 patients (73.6 %) were extubated directly from HFOV without the need of further mechanical ventilation. Five patients had to be reintubated and ventilated by CMV for recurrent episodes of apnea during episodes of late infection in the HFOV group. The average duration of conventional ventilation after reintubation in these 5 patients was 8.6 days.

There were no differences in CNS morbidity. The incidence of grade I-II IVH was the same (13/19, 68.4 % vs 12/18, 66.6 %) and the incidence of grade III-IV and cystic stage of periventricular leucomalacia was also similar (2/19, 10.5 % vs 2/18, 11.1 %). No intergroup differences were found in the incidence of PDA treated with indomethacin. There was no significant difference in stages 1 and 2 ROP. Stages > 2 were 50 % lower in the HFOV group but the difference was not statistically significant (Table 4).

Table 2 Surfactant dosing and postnatal steroid therapy. Values are median (95 % confidence limits

	HFOV group	CMV group
Surfactant		
No. of doses in all patients	0 (0, 3)*	2 (0, 4)
Doses		
No. of patients who did not receive surfactant	11/19 (57.8 %)*	1/18 (5.6 %)
No. of doses in patients who received surfactant	1.5 (1, 3)	2 (1, 4)
Postnatal steroids		
Cumulative dose (mg/kg)	1.6 (0, 11.3)	2.75 (0, 17.5)

* $p < 0.001$

Table 3 Pulmonary outcome. Values are numbers or median (95 % confidence limits)

	HFOV group	CMV group
Airleak		
Pneumothorax	5.3 % (1/19)	5.6 % (1/18)
Pulmonary insterstitial emphysema	10.5 % (2/19)	5.6 % (1/18)
Chronic lung disease		
Clinical score at age 30 days (Toce scale)	4 (0, 5)	4.5 (0, 5)
No. with zero score	5.3 % (1/19)	11.1 % (2/18)
Roentgenographic score	1 (0, 3)*	3 (1, 4)
Clinical score at 36th week postconception (Toce scale)	0 (0, 4)*	2 (0, 10)
No. with zero score	78.9 % (15/19)**	44.4 % (8, 18)
Duration of artificial ventilation (days)	5 (1, 70)	7 (3, 52)
Oxygen use (days)	20 (1, 86)	29 (4, 107)

* $p < 0.003$; ** $p < 0.05$

Discussion

Very premature infants, among them extremely premature infants, were intubated in the delivery room for RDS and immediately randomized into two groups with either HFOV or CMV and then treated with surfactant if defined criteria were fulfilled. The differences between the two treatment groups in terms of ventilator settings, airway pressures, and gas exchange in the acute phase of RDS, the frequency of surfactant and steroid administration, and early and late complications of prematurity were then evaluated.

Thus this study design was very similar to Gerstmann et al.'s Provo Multicenter Trial [8] but with three main differences. One is that the randomly selected treatment was started within 20 min of delivery with no use of the alternative treatment. Second, in our study surfactant was administered after randomization into a treatment group and only if defined criteria were met after initial ventilatory stabilization. Third, our study focused on extremely premature newborns with significantly lower gestational age and birthweight than those of Gerstmann et al. [8]. These prematures are the most likely to benefit from HFOV because of being at high risk of chronic lung disease. Like in Gerstmann et al.'s trial [8], patients with infection were also included in our study. The fact that despite random allocation there was a significantly higher proportion of males in our study may put the HFOV group at a disadvantage compared to the CMV group, especially for the comparison of pulmonary outcomes [13, 14].

Table 4 Clinical outcomes – early and late morbidity (*SEH* subependymal hemorrhage, *PVL* periventricular leukomalacia)

	HFOV group	CMV group
PDA		
Indomethacin-treated	36.8 % (7/19)	44.4 % (8/18)
CNS morbidity		
SEH grade I	42.1 % (8/19)	38.8 % (7/18)
IVH grade II	26.3 % (5/19)	27.7 % (5/18)
IVH grade III	0 %	5.6 % (1/18)
IVH grade IV	0 %	0 %
IVH grade I–II	68.4 % (13/19)	66.6 % (12/18)
PVL, cystic stage	10.5 % (2/19)	5.6 % (1/18)
IVH grade III + PVL (cystic)	10.5 % (2/19)	11.1 % (2/18)
Retinopathy		
Stage I–II	78.9 % (15/19)	66.6 % (12/18)
Stage >II, cryotherapy	10.5 % (2/19), 2	22.2 % (4/18), 4

Recruitment of optimal lung volume was achieved by approximately 30 % higher PA_wDP in the HFOV group in comparison with MA_wP in the CMV group during the early postnatal period. A higher PA_wDP in the HFOV group was the logical result of the optimal lung volume strategy which is an accepted method of improving oxygenation and a prerequisite for good ventilation [15]. This 30 % increase in PA_wDP was higher than reported in other studies or than generally applied. Better

oxygenation, if expressed as A-aDO_2, an indirect reflection of ventilation-perfusion mismatch, was achieved in the HFOV patients during the first 14 h after the start of mechanical ventilation. Our results are in agreement with other studies [8] and confirm the improvement in ventilation – perfusion matching in patients with RDS [16–18]. However, if oxygenation was expressed as oxygen index, there was no difference between the groups due to the fact that in calculating oxygen index in the HFOV group, the higher PaO_2 values in the denominator were offset by the higher mean airway pressure in the numerator.

Fewer patients in the HFOV group needed surfactant treatment after HFOV was used to recruit optimal lung volume. This could be explained by better oxygenation achieved with higher PDA_wP and lung volumes so that the gas exchange-based criteria for surfactant treatment were not met. Another explanation for less need for surfactant, not tested in this study, might be the reduction of pulmonary injury, as reported in animal experiments using combined treatment of surfactant and HFOV [20, 21]. Animal studies have demonstrated less inflammatory reaction in the lungs and less hyaline membrane formation with lower protein influx into alveoli from capillary protein leak during HFOV [22, 23]. On the other hand, the phasic tidal volume changes in CMV are believed to induce these pathophysiologic changes in the lungs [24]. In our study, starting HFOV before any other conventional respirator treatment may have contributed to avoiding significant lung injury and to reducing the need for surfactant during the acute phase of RDS in these premature newborns. However, larger studies and the inclusion of early markers of lung injury would be required to test this hypothesis.

The lower roetgenographic and clinical scores for assessment of chronic lung disease in our HFOV group, which was given less surfactant, also suggest a reduction in pulmonary injury. However, this was not supported by the duration of ventilator support and the use of long-term oxygen, neither of which was statistically different at the two times of investigation between the two groups: results contrasting with those of Gerstmann et al. [8] and Clark et al. [7]. This may represent a Type II error due to our smaller population, or reflect differences in study design like including patients with early and late onset of infection. Thus ventilator support required for recurrent apnea as a complication of infection could have biased the total duration of mechanical ventilation in our study.

There were no differences in the incidence of CNS and ROP morbidity between the two groups. Despite the prematurity of the patients, the incidence of serious stages of IVH and higher stages of ROP, which needed cryotherapy, was remarkably low compared to other studies [1, 8]. The two patients initially randomized to the CMV group fulfilled crossover criteria and were treated by HFOV successfully. In Gerstmann et al.'s Provo Multicenter Trial [8] there were also more patients who failed during CMV than during HFOV.

In conclusion, the immediate use of HFOV associated with early achievement and maintenance of optimum lung volume in HFOV is a promising approach in the treatment of RDS in very and extremely premature newborns. It resulted in better oxygenation, less need for surfactant, and a lower incidence of chronic lung disease compared to conventional ventilation. However, prospective randomized studies, where lung volume strategies and optimization of conventional ventilation are pursued early on , are needed.

References

1. HIFI Study Group (1989) High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the management of respiratory failure in preterm infants. N Engl J Med 320: 88–93
2. Arnold JH, Hanson JH, Toro-Figuero LO, Gutiérrez J, Berens RJ, Anglin DL (1994) Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med 22: 1530–1539
3. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K, Oguchi K, Togarih, Nishidah, Mishina J (1993) A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. Early Hum Dev 32: 1–10
4. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, Redding GJ, DeLemos RA, Sardesai S, McCurnin DC, Moreland SG, Cutter GR, Abman SH (1997) Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 131: 55–62
5. DeLemos RA, Yoder B, McCurnin D, Kinsela J, Clark R, Null D (1992) The use of high-frequency oscillatory ventilation and extracorporeal membrane oxygenation in the management of term/near term infant with respiratory failure. Early Hum Dev 29: 299–303
6. Carter JM, Gerstmann DR, Clark RH, Snyderg, Cornish JD, Null DM, DeLemos RA (1990) Extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 85: 159–164
7. Clark RH, Gerstmann DR, Null DM Jr, DeLemos RA (1992) Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 89: 5–12

8. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Bertrand JM, Battisti O, Langhendries JP, Francois A, Clark RH (1996) The Provo Multicenter Early High-frequency Oscillatory Ventilation Trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 98: 1044–1057
9. HiFO Study Group (1993) Randomized study of high frequency oscillatory ventilation infants with severe respiratory distress syndrome. J Pediatr 122: 609–619
10. Papile LA, Burstein J, Burstein R, Koglerh (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 92: 529–534
11. Toce SS, Farrell PM, Leavitt LA, Samuels DP, Edwards DK (1984) Clinical and roentgenographic scoring system for assessing bronchopulmonary dysplasia. Arch Pediatr Adolesc Med 138: 581–585
12. Committee for the classification of retinopathy of prematurity (1987) II. The classification of retinal detachment. Arch Ophthalmol 1987; 105: 906–912
13. Farrell PM, Avery ME (1975) State of the art HMD. Am J Respir Crit Care Med 111: 657–688
14. Fleischer B, Kulovich MV, Hallman M, Gluck L (1985) Lung profile: sex difference normal pregnancy. Obstet Gynecol 66: 327–330
15. Bond DM, McAloon J, Froese AB (1994) Sustained inflations improve respiratory compliance during high-frequency oscillatory ventilation but not during large tidal volume positive-pressure ventilation in rabbits. Crit Care Med 22: 1269–1277
16. Barnhart SL, Czervinske MP, Meredith KS (1995) High-frequency ventilation. In: Perinatal and pediatric respiratory care. Saunders, Philadelphia, pp 357–375
17. Suzukih, Papazoglou K, Bryan AC (1992) Relationship between PaO2 and lung volume during HFOV. Acta Paediatr Jpn 34: 494–500
18. Ralph DD, Robertson HT, Weaver LF (1985) Distribution of ventilation and perfusion during positive end-expiratory pressure in the respiratory distress syndrome. Am J Respir Crit Care Med 131: 54
19. Claris O, Basson E, Lapillonne A, Besnier S, Picaud JC, Salle BL (1995) High frequency oscillatory ventilation followed by surfactant therapy. A preliminary report. Biol Neonate 67: 315A
20. Froese AB, McCulloch PR, Sugiura M (1993) Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. Am J Respir Crit Care Med 148: 569–577
21. Jackson JC, Truog WE, Standaert TA, Murphy JH, Juul SE, Chi EY, Hildebrandt J, Hodson WA (1994) Reduction in lung injury after combined surfactant and high-frequency ventilation. Am J Respir Crit Care Med 150: 534–539
22. Jackson JC, Truog WE, Standaert TA (1991) Effect of high-frequency ventilation on the development of alveolar edema in premature monkeys at risk for hyaline membrane disease. Am J Respir Crit Care Med 143: 865–871
23. Matsuoka T, Kawano T, Miyasaka K. Role of high-frequency ventilation in surfactant-depleted lung injury as measured by granulocytes. Copyright 1994 the American Physiological Society. Address for reprint requests: K. Miyasaka, Dept. of Anesthesia & ICU, National Children's Hospital, Pathophysiology Research Laboratory, National Children × s Medical Research Center, 3–35–31 Taishido, Setagaya, Tokyo 154, Japan
24. Imai Y, Kawano T, Migasaka K, Takata M, Okuyama K (1994) Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation. Am J Respir Crit Care Med 150: 1550–1554