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High-frequency ventilation and conventional mechanical ventilation in newborn babies with respiratory distress syndrome: a prospective, randomized trial

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Abstract. *Objective.* Morbidity and mortality remain high amongst babies ventilated for a respiratory distress syndrome (RDS). Whether newly developed ventilators allowing high frequency ventilation such as high frequency flow interrupted ventilation (HFFIV) could decrease the morbidity and the mortality was investigated in a randomized study.
Design: Preterm babies weighing ≤ 1800 g suffering from RDS and ventilated by conventional mechanical ventilation (CMV) were randomized to be further ventilated either by CMV (group CMV) or by HFFIV (group HFFIV) when peak inspiratory pressure (PIP) on CMV was ≥ 20 cmH_2O.
Setting: The study was undertaken in the neonatal intensive care unit of the Erasmus Hospital.
Patients: 24 patients entered into the investigation and were randomized but 2 patients were removed from the study because the switch over to HFFIV failed. Eight of the 12 CMV patients and 5 of the 10 HFFIV patients completed the study.
Measurements and results: Clinical variables, blood gas analysis and ventilatory variables were looked at. There were no differences in mortality, in incidence of air leaks and pulmonary complications or in blood gas analysis. Bronchopulmonary dysplasia was not decreased by the use of HFFIV.
Conclusion: It is concluded that HFFIV is safe although it offers no concrete advantages over CMV when applied as we did in a low pressure approach.

Key words: Ventilation – High-frequency ventilation – Respiratory distress syndrome – Preterm – Newborn babies

Premature babies are prone to respiratory failure and often require mechanical ventilation. Assisted ventilation sometimes fails to sustain adequate gas exchange and induces complications such as pulmonary air leaks and bronchopulmonary dysplasia due to barotrauma and oxygen toxicity.

Some studies in newborn babies suffering from respiratory distress syndrome have shown improvements in gas exchange with or without lower airway pressure when high-frequency ventilation (HFV) is used and this with different types of HFV: flow interrupters [1–3], jet ventilation [4–7] and oscillators [8–14]. The present study was undertaken to examine the differences in immediate and later outcome amongst babies ventilated for a RDS by conventional mechanical ventilation and randomized to high-frequency flow interrupted ventilation (HFFIV) or to conventional mechanical ventilation (CMV) when the peak inspiratory pressure had reached 20 cmH_2O or more.

Methods

Patient selection

All newborn infants admitted to the Neonatal Intensive Care Unit (NICU) from October 1988 to October 1990 who required mechanical ventilation entered the study if the following criteria were observed: 1) respiratory distress syndrome due to hyaline membrane disease and exclusion of a pulmonary infection; 2) birth weight ≤ 1800 g; 3) peak inspiratory pressure (PIP) ≥ 20 cmH_2O on conventional mechanical ventilation (CMV) to obtain normal blood gases. Criteria to start conventional mechanical respiratory support used in the unit are a $PaCO_2 > 60$ mmHg or a $PaO_2 < 50$ mmHg for $FIO_2 \geq 60\%$ or a pH < 7.25. Nasotracheal intubation was facilitated by intravenous atropine and muscle relaxation. After entry criteria to the randomization were met, 24 babies were assigned to remain on CMV (group 1) or to be ventilated on HFFIV (group 2) according to a table of random numbers. The study design was approved by the Ethic Committee of the Erasmus Hospital. Parents' formal consent to enter the trial and random assignment to CMV or HFFIV was not sought because both types of ventilators were already used in the unit for more than 10 years for CMV and 2 years for HFFIV. Parents were given information and encouraged to ask questions at any time. No surfactant was used in the study as surfactant was not available in Belgium at that time. No weight stratification was done.

The defined criteria for treatment success were:
- Improvement of gas exchange at lower PIP.
- Succesful switch over from CMV to HFFIV.
- Decreased mortality, pulmonary and neurologic complications.
- Survival without bronchopulmonary dysplasia.

The defined criteria for treatment failure were:

- Acute deterioration, demonstrated by sudden worsening of the patient's status during the ventilation with the ventilator indicated by the randomization so that continued participation in the study would be contrary to the patient's best interest.

HFFIV was introduced in the unit in October 1986 [3] and used routinely as a rescue technique since then. Three study supervisors supervised the management of the HF ventilator very closely.

Ventilator description

All ventilators were checked by the nursing staff every 2 h according to a checklist where ventilation settings and patient related variables (FIO_2, f, PEEP, I/E PIP, Paw) were checked. The target blood gas values for both groups were PaO_2 50–70 mmHg, $PaCO_2$ 35–45 mmHg and pH 7.30–7.40.

1. Conventional mechanical ventilator. CMV was provided by a time-cycled, pressure-limited ventilator Bourns BP 200 respirator (Bourns Inc., Riverside, Calif.) or to a BP 2001 Bear cup (Bear medical systems, Inc., Riverside, Calif.). CMV was delivered at rates of 20–120 cycles/min.

Levels of PEEP were begun at 3 cmH_2O and increased up to 5 cmH_2O. Humidification and heating were provided by a humidifier (Conchaterm II, RCI, Arlington, IL.). The PIP settings were guided by adequacy of chest wall movement and gas exchange. Levels of Paw were measured at the proximal airway by the pressure monitor included in the ventilator.

2. High-frequency ventilator. High-frequency flow interrupted ventilation (HFFIV) was delivered by a high-frequency flow interrupted ventilator (Bird space technologies, Percussionaire Corp., Sandpoint, ID., BIRD VDR_4), consisting of a time-cycled, pressure-limited, pneumatically driven ventilator: the ventilator has been described by Gaylord et al. [1] and by Pfenninger and Gerber [2]. The device delivers gas from a pressurized source (40 psi) through a pneumatic cartridge system. The source gas is interrupted repetitively to produce a pulsatile flow which is placed into the breathing circuit proximal to the patient's airway via an exhalation valve. In the exhalation valve, warmed, humidified gas is entrained to augment tidal volume. Tidal volume delivery, therefore, is determined by flow velocity, inspiratory duration and supplementary gas entrainment. The high-frequency flow interrupted ventilator is composed of 2 ventilator systems, conventional and high-frequency. The conventional component can deliver from 0–70 breaths per minute with independent control of inspiratory time and pressure. The high-frequency component allows programming of frequencies form 0.5–30 Hz and amplitudes from 0–100 cmH_2O. Independent control of the inspiratory to expiratory ratio is possible. Continuous positive airway pressure or positive end-expiratory pressure can be programmed for both systems. As a multitude of varying respiratory programs can be selected, a program was chosen where the amplitude of PIP and PEEP was adjusted to achieve a PIP and PEEP equal to PIP and PEEP on CMV. The percussions were interrupted to obtain the same rhythm as on CMV. Percussive frequency was increased to improve oxygenation and decreased to improve CO_2 elimination. The length of the expiratory time of the percussion was chosen to obtain the lowest mean airway (Paw) possible and a step and backstep type of curve was used. Low PaO_2 levels were corrected first by increasing the FIO_2 then by increasing the frequency up to 700/BPM and then by increasing the PIP. High $PaCO_2$ levels were corrected first by decreasing the frequency down to 400 BPM, then by increasing the PIP, then by increasing the number of cycles/min (more frequent pauses) and then by increasing the expiratory time of the percussion. Levels of Paw were also measured at the proximal airway by the pressure monitor included in the ventilator. Weaning from the VDR 4 was obtained by reducing the PIP and then by increasing the expiratory time of the cycle and gradually reducing the amplitude of the percussion to zero and by maintaining a PEEP of 2–3 cmH_2O. Between tracheal suctions, attempts were made not to use handbagging but to connect the baby to the VDR 4 immediately after suction. A low pressure approach dominated the trial.

Monitoring

All babies were monitored conventionally. Different variables were followed continuously: transcutaneous PO_2 (Tc PO_2), arterial oxygen saturation, arterial blood pressure and differential temperature (core-toe).

Umbilical vein and arterial catheters were inserted to allow continuous blood pressure monitoring and blood gas analysis. In case of failure to place an umbilical arterial catheter, a radial catheter was inserted. Pancuronium and morphine were given intravenously when $FIO_2 \geq 60\%$ (50 µg/kg/dose of pancuronium and 0.1 mg/kg of morphine 3 times a day). Blood gas analysis was performed regularly according to the standards used in the unit.

All the patients had cranial sonography at day 1, 2, 3 and 7 of life and then once a week until discharge.

Random assignment

When PIP ≥ 20 cmH_2O was reached on CMV, according to a table of random numbers, the baby was either maintained on CMV or switched to HFFIV. Blood gas analyses were performed on CMV just at the time of assignment and then 1, 6, 12, 24, 48 and 96 h after randomization. If any patient failed to be switched over to HFFIV, he was then further ventilated by CMV but was removed from the study. The switch over to HFFIV was done by one of the study supervisors.

Statistical analysis

Different variables, biological and clinical, were compared just before and after assignment. This was also done for variables concerning ventilation. The non-parametric Mann-Whitney test was used to compare quantitative data between groups and the Fischer exact test was used to compare the incidence of certain medical complications between groups.

Definitions

Bronchopulmonary dysplasia was defined as chest radiograph showing cystic changes or hyperinflation [15] or oxyen requirement beyond 28 days of life [16] or oxygen requirement at gestational age of 36 weeks [17]. Cerebral hemorrhages and periventricular leucomalacia were defined following Fawer's criteria [18].

Results

During the study period 24 patients were entered into the investigation but of these 24 patients, 2 were removed from the study because the switch over to HFFIV failed: these 2 patients desaturated immediately and the desaturation could not be corrected by changing the conditions of the ventilator.

Table 1 depicts the patient population with the pretreatment variables and the ventilation variables at time of randomization: PIP was very high at time of randomization in both groups and slightly higher in the HFFIV group than in the CMV group but this is not statistically different. The analysis of pretreatment variables demonstrated no appreciable differences between the 2 groups except for birthweights, the heaviest babies being in the HFFIV group. However, gestational ages were the same in the 2 groups. The only statistically significant difference noted was FIO_2 at time of randomization, FIO_2 being higher in the HFFIV group although PaO_2/FIO_2 was not statistically different.

Table 2 depicts the clinical results and ventilatory variables: no statistically significant differences appeared. Two grade III IVH were present on day 2 and 3 and were the reason of death for 2 patients of group CMV and one

Table 1. Patient population and ventilation variables at time of randomization

	CMV	HFFIV	*P*
Number	12	12	
Failure	0	2	
Gestational age (weeks)	29.2 ± 1.96 (26 – 32)	29.8 ± 1.5 (27 – 32)	NS
Birthweights (g)	1194 ± 237 (780 – 1470)	1454 ± 197 (1100 – 1680)	< 0.05
APGAR			
1′	5.1 ± 2.5	4.3 ± 2.5	NS
5′	7.6 ± 2.1	7.4 ± 0.9	
Girls/boys	5/7	3/7	
Length of life at intubation			
(min)	361 ± 835	118 ± 206	NS
(h)	6.0 ± 13.9	1.9 ± 3.4	
PIP cmH_2O	24.3 ± 8.6	27.4 ± 9.8	NS
FIO_2	86.1 ± 16.8	98.8 ± 3.3	< 0.05
PaO_2 (mmHg)	58.2 ± 20.4	62.6 ± 18.4	NS
PaO_2/FIO_2	0.72 ± 0.24	0.68 ± 0.16	NS
$PaCO_2$ (mmHg)	48.5 ± 15.3	44.6 ± 12.6	NS
pH	7.24 ± 0.12	7.31 ± 0.09	NS

Table 2. Clinical results and ventilatory variables

	CMV ($n = 12$)	HFFIV ($n = 10$)	*P*
Deaths	4	5	NS
IVH (I-II-III)	2	1	NS
PVL	0	1	NS
Renal insufficiency	2	3	NS
Air leaks	7	6	NS
pneumothorax	3	5	NS
pneumoperitoneum	1	1	NS
pneumomediastinum	1	1	NS
interstitial emphysema	5	5	NS
air embolism	0	1	NS
Atelectasis	4	6	NS
Stenosis (bronchial, tracheal)	0	0	NS
Plugs	0	2	NS
Lung infection	4	4	NS
Tracheobronchitis	0	0	NS
Duration of ventilation (h)	331 ± 267	307 ± 176	NS
Highest PIP 1st day of life	32.1 ± 9.6	42.6 ± 13.5	NS

Table 3. Pulmonary complications amongst survivors

	CMV *n*	(%)	HFFIV *n*	(%)	*P*
Survivors	8		5		NS
Radiological bronchodysplasia	5	(62.5)	5	(100)	NS
Oxygendependency at 28 days of life	5	(62)	4	(80)	NS
Oxygendependency at 36 weeks of gestation	2	(25)	2	(40)	NS

grade III IVH was present on day 3 in a survivor of group HFFIV. An extremely extended cerebral ischaemia was observed on day 15 in one patient of group HFFIV and led us to stop the vital support with the parents' consentment.

Table 3 depicts the pulmonary complications amongst survivors: no statistically significant differences were noted. Radiological signs of bronchopulmonary dysplasia were more often found in HFFIV ventilated babies than in CMV ventilated babies as was oxygen dependency at 28 days of life and at 36 weeks of gestation but this is not significant. Four patients died in group 1 and 5 patients died in group 2. The reason of death for the 4 patients of group 1 were: severe hypoxemia (day 1 : 1 case), IVH (day 2 and 3 : 2 cases) and MOF (day 21 : 1 case). The reason of death for the 5 patients of group 2 were severe hypoxemia (day 1 : 2 cases), massive cerebral ischemia (day 15 : 1 case) and MOF (day 16 and 24 : 2 cases).

Figure 1 shows the evolution after randomization of PIP, $PaCO_2$ (mmHg), PaO_2/FIO_2. FIO_2 is slightly higher at the time of randomization in the HFFIV group but PaO_2/FIO_2 is the same. After randomization, the PIPs are higher in the HFFIV group at 48 and 96 h of randomization ($p < 0.01$): the highest PIPs are observed in the HFFIV group. There are no statistically significant differences for pH, PaO_2, PaO_2/FIO_2 but $PaCO_2$ are lower with HFFIV than with CMV at 12 h of randomization ($p < 0.05$). No deleterious effect on hemodynamic was observed when preterm babies were put on HFFIV.

Discussion

High-frequency ventilation has been used in several neonatal conditions such as severe RDS, pulmonary interstitial emphysema, neonatal pulmonary hypertension and applied very often in an uncontrolled manner, with different selection criteria [12, 19–21]. The purpose of this small randomized study was to find out whether HFFIV is a safer method of ventilatory support than CMV in newborn preterm babies suffering from a severe RDS.

As it is easy to use a parameter of ventilatory support in clinical practice routine to compare babies, a level of 20 cmH_2O or more was chosen to randomize the babies without exposing to undue risks the newborn babies who would normally have survived without HFFIV. When the results are analysed, we can observe that the switch-over from CMV to HFFIV was successful in 10 cases out of 12 (83%). HFFIV did reduce neither the overall mortality, nor the pulmonary or neurological complications. The incidence of BPD in survivors was the same and gas exchange was not improved except for $PaCO_2$ after 12 h of HFFIV but not later on.

The HFFIV group was perhaps slightly sicker than the CMV group as, at randomization, PIP was slightly higher (not significantly) and FIO_2 used to oxygenate these babies was statistically higher ($p < 0.05$). However the PaO_2/FIO_2 ratio was the same. Statistically significant higher PIPs were used with HFFIV after 48 and 96 h of randomization to obtain the same gas exchange. Unfortunately we did not have the capability to measure the Paw in the same way with both kinds of ventilators. Up to 1991, a low volume/pressure approach dominated the trials where HFV was used. At the time the HIFI trial was conceived, a great deal [22] had been written about the low peak pressures and very little about the importance

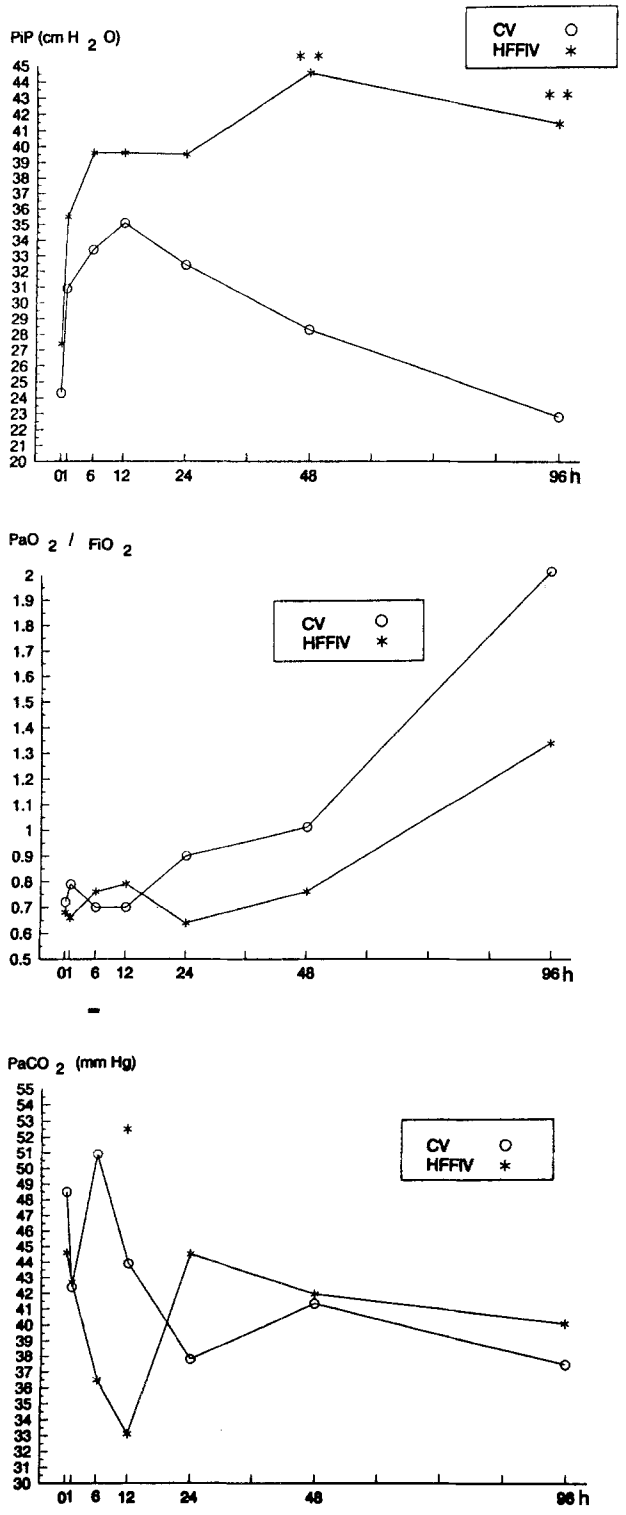

Fig. 1. Evolution over time of PIP (cmH_2O), $PaCO_2$ (mmHg), PaO_2/FIO_2. $^*p<0.05$; $^{**}p<0.01$

of mean airway pressure and mean lung volume. The HIFI trial showed, as our study, no reduction of bronchopulmonary dysplasia. Since then, studies [21, 23] where an early recruitment with a high volume strategy has been used with HFOV, have shown a marked reduction of bronchopulmonary disease.

The incidence of IVH was very low in our study: 16% (CMV) and 10% (HFFIV) instead of 42% (CMV) and 40% (HFOV) in the HIFI study. The high incidence of IVH during HFOV in the HIFI study has been ascribed to the large changes in $PaCO_2$ during HFOV or to a restricted venous return to the heart. No deleterious effect on venous return was noted with HFFIV. The use of the VDR_4 and the use of HFFIV is not common in human babies. A few papers have shown [1, 2] an improvement in blood gas exchange (18 patients) but these 2 studies were not randomized. HFJV and HFOV have been more studies. Polak et al. [24] have shown that the histopathological lesions were similar in 6 patients reciving HFJV for more than 90 h and in 6 patients receiving CMV.

Some animal studies do show a preventive protective effect of HFV either in baboons [25] and in monkeys with HFOV [26], or in rabbits with HFJV [27]. Some animal studies do not show a protective effect of HFFIV [28] but in these studies, HFFIV was used continuously. In 1990, Wiswell [29] showed that HFFIV induces more tracheobronchial lesions after 8 h of ventilation when it is used without pauses than when it is used with 10 pauses/min: this way of using HFFIV was completely different from ours.

The necessity to avoid CMV before HFV and to randomize newborn babies per pathology immediately after intubation taking into account different factors known to, or supposed to, change the development of the BDP such as handbagging, humidification, administration of surfactant is still needed. The way we worked was certainly designed to minimizre peak airway pressures as we believed that pressure was bad and that high Paw had to be avoided.

A high volume strategy with either a high Paw approach or sustained inflations would probably induce a better recruitment and would perhaps avoid, if used from birth onward, the development of hyaline membrane disease in surfactant-deficient lungs with a possible increased risk of air leaks and hemodynamic instability due to the use of higher intrathoracic pressures.

In summary, our study demonstrated that although HFFIV can be applied safely in preterm infants with severe RDS, it does not prevent or reduce barotrauma and does not substantially improve the outcome when used with a low pressure approach. However, we think that HFFIV merits further investigations with a high volume strategy.

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