High Frequency Percussive Ventilation: Principle and Fifteen years of experience in preterm infants with respiratory distress syndrome.

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Key words: High frequency percussive ventilation · Premature infants · Respiratory distress syndrome

Abbreviations CLD chronic lung disease · CMV conventional mechanical ventilation · HFPV high frequency percussive ventilation · IVH intraventricular haemorrhage · mean Paw main airway pressure · PIP peak inspiratory pressure · PEEP positive end-expiratory pressure · RDS respiratory distress syndrome.

ABSTRACT

We evaluated the safety and efficacy of high frequency percussive ventilation (HFPV) as a ventilation mode in premature infants (gestational age ≤32 weeks) with respiratory distress syndrome (RDS). In a first study a prospective randomized trial was conducted to compare the effects of HFPV with conventional mechanical ventilation (CMV) in neonates (n = 52) from 1986 to 1989. This study was followed by a retrospective analysis (from 1989 to 1998) of 273 consecutive neonates exclusively ventilated with HFPV. In the third part of the study (from 1998 to 2002) 55 infants on HFPV, of whom 22 treated with surfactant as rescue therapy, were retrospectively studied. In part 1, the HFPV group had a lower incidence of pulmonary air leak (8% vs 33%, $p<0.05$), intraventricular haemorrhage (IVH) (8% vs 37%, $p=0.02$) and chronic lung disease (CLD) assessed at 28 days (15 vs 43 %, NS) and 36 weeks gestational age (0% vs 29%, $p<0.02$), than the CMV group. Mortality was also lower in the HFPV group (20 vs 48 %, $p<0.04$). Survival rate in part 2 and 3 of the study was 85 and 89 % respectively, with an identical incidence in air leak (9%). The incidence of IVH (12 vs 9 %) and CLD at 36 weeks gestational age (3 vs. 4 %) was similar in both groups. We conclude that high frequency percussive ventilation is a safe and effective ventilation technique, and results in a favourable pulmonary outcome in preterm infants with RDS.

The 1960's marked the development of reliable positive pressure ventilators, which were considered to offer a significant advance in the care of newborns with respiratory distress. Despite the life-saving potential of medical respirators, there is considerable experimental and clinical evidence that mechanical ventilation in itself, if not properly managed, can also cause or exacerbate lung injury resulting in so-called "ventilator-induced lung injury"[1,2]. However, understanding techniques and tools that are available to use with mechanical ventilation would better serve the clinician and patient in order to achieve better care. During mechanical ventilation of the lung, there are evident goals that practitioners will strive to meet: 1) ventilator-induced lung injury should be avoided; 2) oxygen toxicity should also be kept to a minimum.

Respiratory distress syndrome remains associated with a significant mortality rate. While there have been certain encouraging results secondary to ventilation management using lung protective strategies, their potential benefits may be limited. Moreover, relatively large tidal volumes are still mandated in some patients to ensure adequate gas exchange. In the face of such known clinical barriers, it is reasonable to expect that physicians and clinical investigators will continue to search for new, more effective ventilator techniques.

Starting in the late 1970's, the interest in High Frequency Ventilation (HFV) has experienced repeated cycles of excitement followed by waning. The increasing evidence that conventional mechanical ventilation (CMV) contributes to lung injury has lead to a recent resurgence of interest in the clinical

applications for high frequency ventilatory regimens.[3,4] There now exists a substantial base of experimental and clinical data relative to the effectiveness and safety of this ventilatory technology.[5,6]

HFV enhances the mechanical mixing of intrapulmonary gases, creating a major diffusive component, which serves as an important adjunct to convective CMV in the management of preterm and term newborns who have respiratory failure. Animal data suggests that the early application of HFV modifies the sequence of lung injury that can be initiated by CMV.[7,8] However, the results of High Frequency Oscillatory Ventilation (HFOV) clinical trials question whether or not HFOV can prevent chronic lung disease in preterm infants.[9-14]It must be accepted that the etiology of chronic lung disease in preterm infants remains multifactorial and often complex.[15,16] The mechanics of the lung during high frequency ventilation have been studied, creating additional uncertainties. The physiology and pathophysiology of gas exchange during high-frequency ventilation has proven to be elusive and often controversial. Questions also remain relative to the risk-benefit ratio for HFOV, such as to whether or not ventilatory strategies influence the risk of neurological complications. Therefore, the development of ventilation and oxygen-exposure strategies that minimize lung injury, are a priority for improving outcomes. These strategies have to be employed, not only to help recruitment, but also to prevent derecruitment.

High Frequency Percussive Ventilation (HFPV) is a hybrid form of high frequency ventilation, conceived by Dr. Forrest M. Bird (Percussionaire® Corp. Sandpoint, ID.USA) in the early 1980's. The concept of pneumatic high-energy percussive ventilation combined diffusive/convective component and not related to high frequency vibration, jet insufflations or electronically controlled crank or magnetically dynamic oscillators. The concept for HFPV was truly a novel concept, directed toward maximizing mechanical ventilation "in all patient populations" while providing for major lung protection strategies.[6]

Volumetric Diffusive Respiration (VDR) is the intensive care version of HFPV. The VDR concept combines the beneficial effects of high frequency ventilation and conventional mechanical ventilation. The VDR is a pneumatically powered, pressure limited, time-cycled diffusive/convective ventilator. Inspiration (I) consists of the progressive accumulation of subtidal breaths, which allows a gradual increase in pulmonary airway pressure thus gradually increasing lung volume, culminating in an oscillatory plateau (oscillatory equilibrium). This is followed by the passive exhalation of a tidal volume (E). The VDR combines CMV and HFV, to create convective exchange delivery rates from 0 to 70 breaths per minute, with selectable inspiratory/expiratory ratios. Concomitantly, separate percussive high-frequency breaths with frequencies of from 0.5 to 20 Hz are continuously delivered. Essentially the lungs are being ventilated with a continuous percussive subtidal diffusive gas exchange while the convective lung volume changes in a sinusoidal wave format. Mechanically generated airway delivery pressures are measured at the proximal airway. Figure 1, illustrates a typical waveform that can be scheduled with a HFPVentilator.

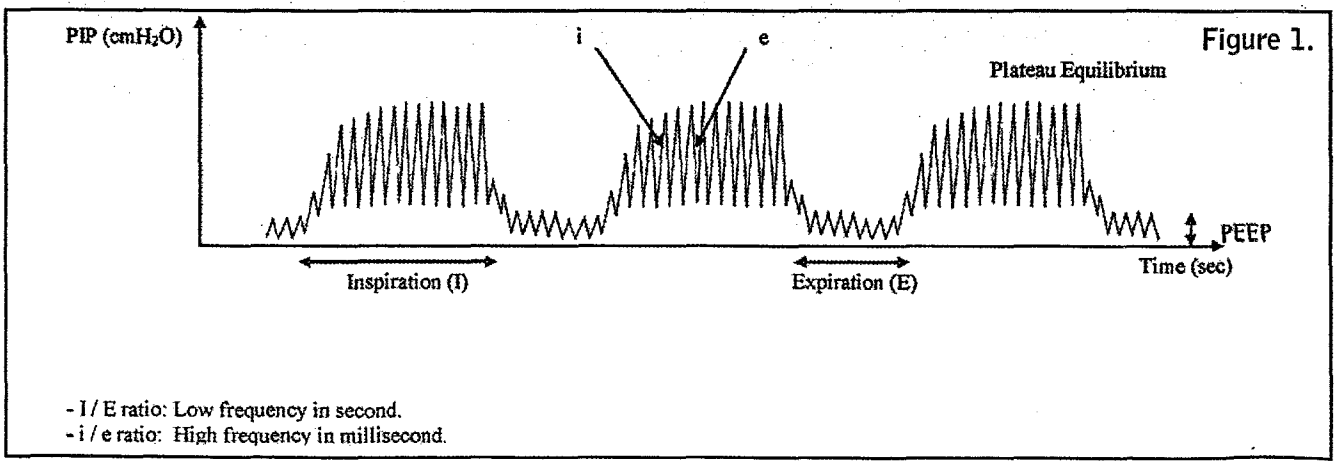


Figure 1.

Legends: Typical HFPV waveform

The most unique feature of the HFPV breathing circuit is the Phasitron, which provides for the patient's physical/physiological airway interface through which pulsatile flow is delivered into the lungs (figure 2).

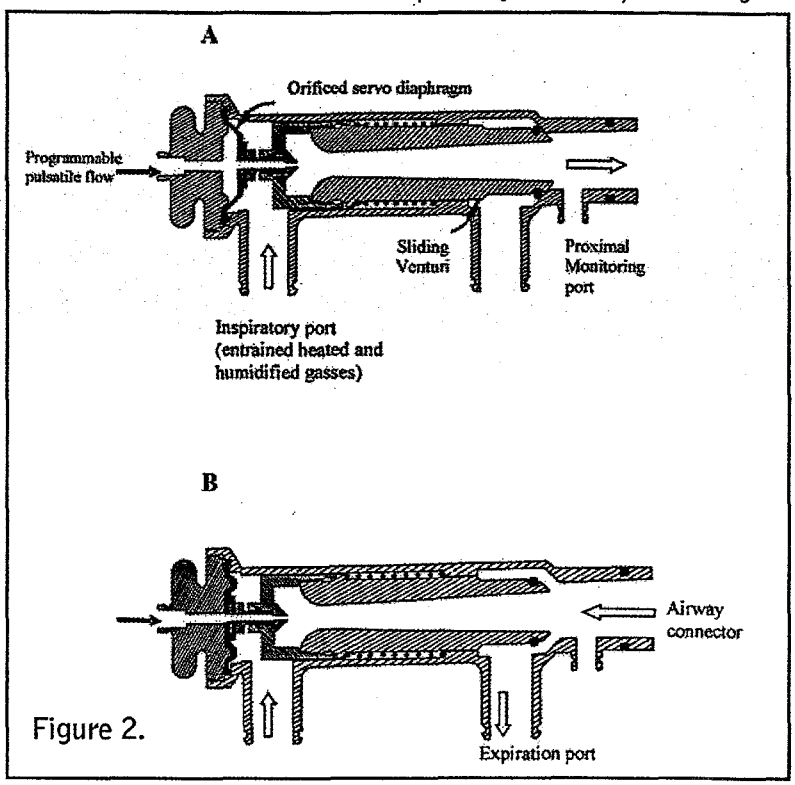


Figure 2.

Legends: The Phasitron, patient ventilator interface:

The sliding venturi used during High Frequency Percussive Ventilation in the Closed (inspiratory) and open (expiratory) positions. During inspiration (A),pulsatile flow from the ventilator fill the space above the orificed servo diaphragm and cause the venturi to slide forward. During expiration (B), the venturi is not pressurised, which allows free expiration of gases through the expiratory port. The sliding venturi operates as inspiratory, expiratory valves all in one.

In essence, the Phasitron becomes the patient's respirator being positioned at the patient's proximal airway. The proximal airway location of the Phasitron eliminates the compliance of the humidification section of the breathing circuit. Additionally, failsafe ambient-vented intake and exhaust valves are a component of the Phasitron permitting the spontaneously breathing patient low dead space access to ambient air.

Using the Venturi and Bernoulli theories, warmed and humidified gases can be entrained through the breathing circuit by the entrainment port of the Phasitron. The sliding venturi of the Phasitron is regulated in such a manner that, during inspiration, there is a stepwise increase in airway pressure to the scheduled peak inspiratory pressure (PIP). By the repetitively fracturing the inspiratory flow gradient with a sequence of diminishing high frequency subtidal volume deliveries, the lung volume is progressively increased in a controlled "step ladder" fashion until the programmed PIP (oscillatory equilibrium) is reached. Oscillatory equilibrium is sustained during the entire programmed inspiratory interval (I), followed by passive exhalation (expiratory time) (E). At end of the timed inspiratory interval, the lung is allowed to empty passively until the programmed oscillatory expiratory baseline is reached.

The VDR allows the control of the following variables: 1) PIP, 2) Oscillatory PEEP, 3) CPAP, 4) High (percussive) frequency, 5) inspiratory/expiratory (pulse i/e) ratio, 6) Inspiratory time, 7) Expiratory time and 8) F_{IO2}.

HFPV was introduced in our Neonatal Intensive Care Unit in November 1985. Quickly, it became clear that HFPV eliminated C_{O2} and improved oxygenation extremely effectively. These observations were confirmed by the early studies carried out in neonates with respiratory pathologies as RDS, interstitial pulmonary emphysema, comparing gas exchange during HFPV to CMV.[17,18] At the same time, Hurst et al. using HFPV as a salvage therapy demonstrated a decrease in intracranial pressure (ICP) in 38 patients with head injury and ARDS.[19] In addition, it became clear that HFPV improved gas exchange at an applied mean airway pressure (mean

P_{aw}) lower than CMV. Interesting observations that should be considered for the therapeutic approach of preterm infants with RDS, known to have fragile brain with high risk to develop intraventricular hemorrhage and periventricular leukomalacia.

In this article, we report the successive steps in fifteen years of experience with HFPV and to evaluate whether its use is safe and effective in preterm newborns with RDS. First, a prospective randomized trial (part 1) was conducted, from 1986 to 1989 to compare HFPV with CMV in preterm infants with moderate to severe IRDS. This study was followed by a retrospective analysis (part 2) from 1989 to 1998, based on the results achieved with HFPV to give a survey of outcomes of a large series of patients uniquely ventilated with HFPV, and third (part 3) from 1998 to 2002, to evaluate whether in conjunction to exogenous surfactant, HFPV can further improve outcome.

STUDIES METHODS

PART 1

This prospective randomized study was performed in a Neonatal Intensive Care Unit between March 1986 and July 1989. Parents were informed about both methods of ventilation and gave their informed consent.

Patient selection Patients with gestational age ≤ 32 weeks presenting with a RDS due to hyaline membrane disease and requiring mechanical ventilation within the first 12 hours after birth, were included in the study. Criteria for mechanical ventilation were $P_{aCO2} \geq 60$ mm Hg and /or $P_{aO2} < 50$ mm Hg, with $F_{IO2} \geq 0.6$ during spontaneous breathing. In order to study the severe cases of RDS, only patients requiring ventilation for at least 24 hours with a $F_{IO2} \geq 0.4$ and peak inspiratory pressure (PIP) > 20 cm H_2O were included for statistical analysis. Patients with major congenital malformations, neuromuscular disease or chromosomal anomalies were excluded from the study. Infants were randomized at intubation to be ventilated with HFPV or CMV. The assigned mode of ventilation was maintained until the patient was extubated. Initiation of mechanical ventilation was defined as T_0 and baseline data were collected at this point.

VENTILATION STRATEGIES

For both groups, ventilator settings were adjusted to achieve P_{aO2} values between 55 to 80 mm Hg and P_{aCO2} values between 35 to 45 mm Hg.

Patients assigned to CMV, were mechanically ventilated on pressure-controlled ventilation with a Siemens 900C ventilator (Siemens-Elema, Solna, Sweden). Initial ventilator settings were: respiratory rate between 30 and 60 breaths per minute, inspiratory time between 0.3 and 0.6 seconds with positive end-expiratory pressures (PEEP) of 3 to 6 cm H_2O and PIP sufficient to achieve adequate gas exchange. To improve ventilation, increasing rate (max. ? 60 breaths/minute) was preferred to increasing PIP. Ventilatory adjustments to improve oxygenation were in the following order: increase of inspiratory oxygen fraction followed by increase of the end-expiratory pressure, the inspiratory time or peak inspiratory pressure. Weaning was performed by decreasing PIP first, followed by a reduction in ventilation rate.

With HFPV, Initial ventilator settings were: PIP of 25 cm H_2O, Oscillatory PEEP of 6 cm H_2O, low rate of 40 breaths per minute with a ratio of 1:1, Frequency of 800 cycles per minute with a i/e ratio of 1:2. We considered that the sub-tidal volume generated at frequencies of 600 to 900 cycles per minute provided the necessary margin of safety to achieve and maintain adequate alveolar aeration. Oxygenation was improved by increasing PIP, then F_{IO2}, followed by an augmentation in pulse frequency to 900 breaths per minute, thereby increasing the intrapulmonary diffusion component. Further adjustment included an increase in inspiratory time (I) at oscillatory equilibrium to enhance intrapulmonary gas mixing and establishing a baseline PEEP. Carbon dioxide removal was enhanced by decreasing the high-frequency rate towards 500 breaths per minute, thereby increasing sub-tidal volume and the convective component. Eventually, conventional rate was increased in some patients in order to enhance intrapulmonary convection. Weaning from the VDR was achieved with traditional IMV weaning rules, gradually decreasing PIP and conventional rate, followed by lengthening of the expiratory time (E). Final weaning was done with

PEEP of 2 to 4 cm H_2O to reduce the work of spontaneous breathing.

Criteria for extubation were the same for both groups. After extubation, patients requiring reintubation due to inadequate ventilation and / or oxygenation, were returned to the original assigned ventilator.

MEDICAL TREATMENT

No infants included in the study received exogenous surfactant. Mild sedation with morphine was applied to tolerate ventilation and reduce stress. Muscle relaxants were seldom given, additional treatment (other sedation, inotropic agents, antibiotics and chest physiotherapy) was left to the discretion of the attending intensivist. Symptomatic patent ductus arteriosus was treated with indomethacin or surgical ligation. Hydration and nutrition were provided through an intravenous route.

DATA COLLECTION

In each patient heart rate, arterial blood pressure, pulse oxymetry and transcutaneous P_{02} were registered. Arterial blood gas analysis was performed on regular basis or after each adjustment of ventilator settings until stabilization, and then every 4 to 6 hours or as clinically indicated. Cranial sonography was obtained at day 1, 3, 7, and then weekly until discharge. A cranial sonography before entry could not be performed because of early entry in the study. Chest radiographs were obtained immediately after intubation and then daily or as clinically indicated. All chest radiographs and cranial sonographies were interpreted by a pediatric radiologist not involved in the study.

The following data were collected and recorded for each patient: prenatal steroid administration, gestational age, birth weight, gender, in or outborn, Apgar score at 1 and 5 minutes, age at intubation, severity of lung disease,[20] duration of ventilation and oxygen therapy, air leaks, patent ductus arteriosus, presence and severity of intraventricular

hemorrhage, as well as oxygen requirement at 28 days of life and at 36 weeks of gestational age. We calculated the average ventilator-free days at 28 days after randomization. Patients who died or were mechanically ventilated for more than 28 days were assigned zero ventilator-free days, to correct for differences in early mortality.[21,22]

Primary endpoints were P_{aO2}/F_{IO2}, chronic lung disease (CLD) defined as oxygen requirement at 28 days of life and at 36 weeks of gestational age, air leak and intraventricular hemorrhage as defined by Papile et al.[23] Air leaks included pneumothorax, pneumomediastinum and pulmonary interstitial emphysema. Secondary endpoints were survival, duration of mechanical ventilation, ventilation-free days and length of hospitalization.

The end of the study for a given patient was the time of discharge from hospital or death.

PART 2

Due to the favorable results in part 1 (see results), we took the decision to use HFPV as the primary treatment in infants with RDS. During a ten-year period (1989 – 1998), all consecutive newborn infants who fulfilled the same inclusion and exclusion criteria of the randomized clinical trial were exclusively ventilated with HFPV. The same ventilatory strategies and medical treatment were used as in part 1, no exogenous surfactant was used.

PART 3

When exogenous surfactant (Survanta, Abbott Laboratories, USA or Alvofact, Boerhinger Ingelheim, Germany) became available in our unit, surfactant was given at a $P_{aO2} \leq 60$ mm Hg with PIP ≥ 30 cmH_2O and $F_{IO2} \geq 0.5$, in premature infants with evidence of RDS on a chest radiograph. Surfactant was instilled through a dual-lumen endotracheal tube (Vygon, France) without changing the patients' position or disconnection from the ventilator. If oxygenation did not improve, a second dose of surfactant was given within 12 hours. This part of the study was conducted from 1998 to 2002.

STATISTICAL ANALYSIS

Data are presented as mean ± (SD). Statistical significance was determined with Mann-Withney U-test for nonparametric data and Fisher's exact test for categorical data, as a p value ≤ 0.05. Comparison between study 1, 2 and 3 was performed with ANOVA and Dunn's post hoc test.

RESULTS

PART 1

During the study period, 55 patients were randomized. Two infants were excluded from the study because of severe congenital anomalies (1 CMV, 1 HFPV) and one was withdrawn from the study because of the rapid improvement of the RDS (HFPV). The remaining 52 patients (n=27 in CMV, n= 25 in HFPV) all completed the clinical trial. Both treatment groups were comparable in baseline characteristics (table 1).

Ventilation variables at randomization were similar in the two groups (figures 3 and 4), except for mean P_{aw} Figure 3 shows a statistically significant difference in P_{aO2}/F_{IO2} ratio between both groups after 1 hour of mechanical ventilation ($p< 0.003$), which persists for 72 hours ($p< 0.001$). P_{aCO2} was lower in the HFPV group from 6 to 72 hours after intubation ($p< 0.03$). In the HFPV group mean P_{aw} remained significantly lower throughout the first 72 hours, whereas the difference in PIP was significant after 12 hours of mechanical ventilation (Figure 4). The incidence of air leak and IVH was smaller in the

Table 1 Demographic data and severity of lung disease (at time of randomisation: part 1).

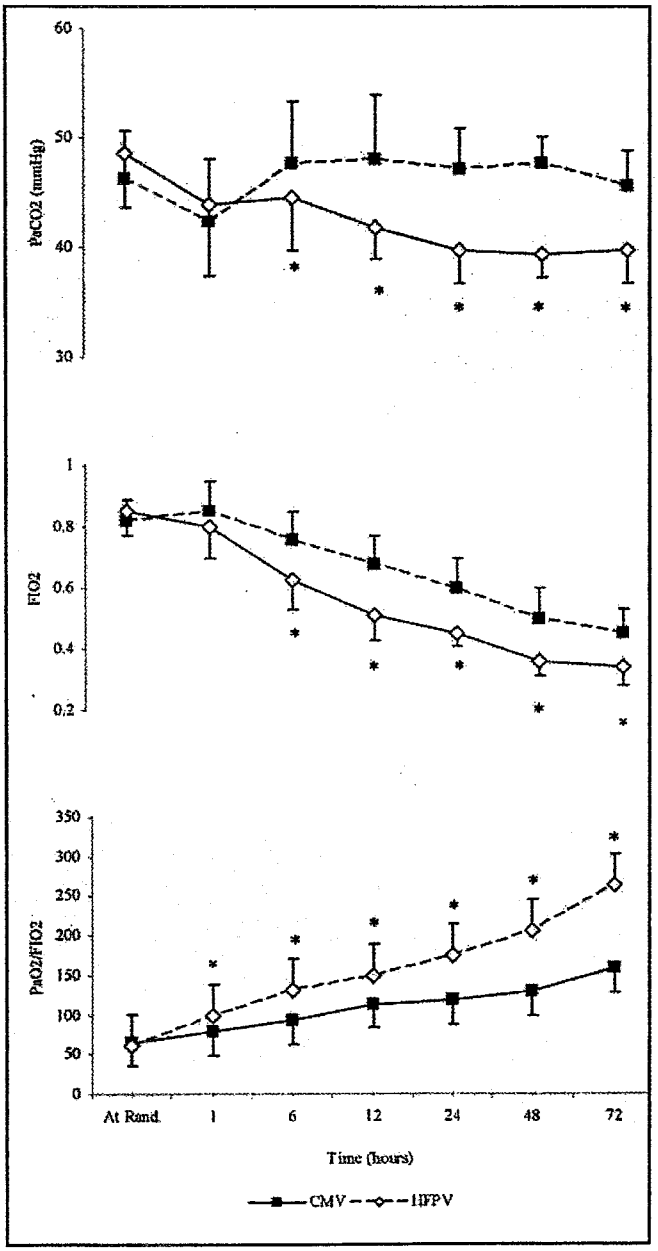
	Part 1 CMV	Part 1 HFPV	Part 2 HFPV	Part 3 HFPV + Surfactant
N patients	27	25	273	55
Prenatal steroïd	8 (30%)	6 (24%)	103 (38%)	35 (64%)
Cesarian section	13 (48%)	11 (44%)	126 (46%)	21 (38%)
Gestational age (wks)	29.8±1.6	30.0±1.6	29.3±1.9	28.2±1.6
Birth weight (gr.)	1389±225	1404±237	1289±243	1140±279
Male / female	17 / 10	14 / 11	147 / 126	24 / 31
Inborn / outborn.	18 / 9	17 / 8	198 / 75	44 / 11
Apgar score at 1 min.	4.2±2.4	4.5±2.4	4.7±1.7	4.9±1.5
Apgar score at 5 min.	7.4±1.0	7.6±1.1	7.4±1.0	7.3±1.0
Age at intubation	3.0±2.7	4.2±3.1	4.7±3.1	3.0±2.9
Radiograph degree HMD (1-4)	2.9±0.6	3.1±0.7	3.0±0.6	2.9±0.6
N patients ≤ degree 2	6 (22%)	5 (20%)	41 (15%)	14 (25%)
N patients > degree 2	21 (78%)	20 (80%)	232 (85%)	41 (75%)

Table 2 Duration of ventilation and clinical outcome.

	Part 1 CMV	Part 1 HFPV	Part 2 HFPV	Part 3 HFPV + Surfactant
N patients	27	25	273	55
Length of hospitalisation among survivors (d)	63.3±16.7	48.5±18.9*	54.7±22.2	67.2±23.9
Survivors to discharge	14 (52%)	20 (80%)*	232 (85%)	49 (89%)
Duration of ventilation (d)	13.2±7.6	9.3±2.8*	9.8±6.9§	8.5±4.9§
Ventilation-free days (d)	8.1±8.9	15.1±8.1†		
N surfactant				22 (40%)
Air leak	9 (33%)	2 (8%)*	26 (9%) §	5 (9%)§
IVH, all grades	10 (37%)	2 (8%)‡	33 (12%)	5 (9%)
IVH, Grade III - IV	6 (22%)	1 (4%)	14 (5%)	2 (3,6%)
PLV	2 (7%)	1 (4%)	8 (3%)	3 (5%)
Symptomatic PDA	4 (15%)	4 (16%)	48 (18%)	9 (16%)

* $p < 0.05$ vs CMV, † $p = 0.01$ vs CMV, ‡ $p = 0.02$ vs CMV, § $p < 0.001$ vs CMV

Figure 3

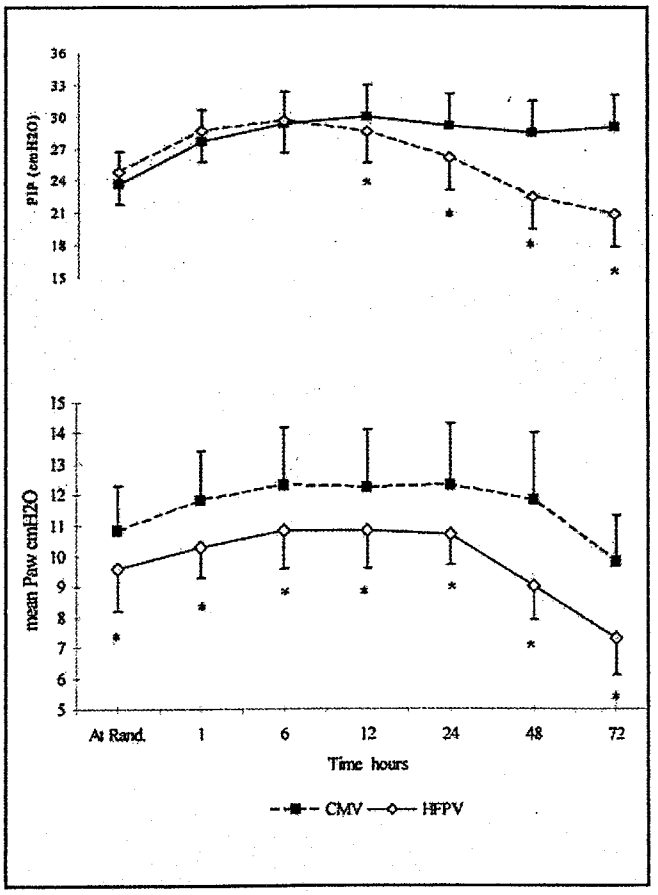


Legends: Evolution over time of PaO2/FIO2, FIO2 and PaCO2 n = 27 (CMV), n = 25 (HFPV), * p < 0.05 vs CMV

HFPV group as well as the duration of mechanical ventilation and the length of hospitalization. Furthermore, the average number of ventilation-free days was significantly higher in the HFPV group (p = 0.01) (table 2).

At 36 weeks gestational age the incidence of CLD was significantly lower in infants assigned to HFPV compared with CMV (0% vs 29%, p< 0.02). Mortality rate was lower in the HFPV group (p< 0.05) (table 3).

Figure 4



Legends: Evolution over time of mean Paw and PIP n = 27 (CMV), n = 25 (HFPV), * p< 0.05 vs CMV

PART 2 AND PART 3

In study 2 a total of 273 consecutive infants were exclusively ventilated with HFPV (same inclusion and exclusion criteria as in part 1). A total of 55 patients were included in study 3, of whom 22 being were treated with exogenous surfactant. Five of them required 2 instillations and one received 3 doses. Surfactant was administered between 180 and 490 minutes after intubation (median 270 min.). The differences in demographic data are illustrated in table 1. The incidence of CLD was statistically significantly higher in the CMV patients in study 1 versus the HFPV patients in study 2 (p<0.003) and study 3 (p<0.02). Similarly, air leak was more frequent in CMV patients in study 1 versus study 2 and 3 (p<0.001, for both groups). Duration of ventilation was significantly longer in CMV patients (study 1) versus patients in study 2 and 3 (p<0.001). There

Table 3 Mortality and pulmonary morbidity among survivors.

	Part 1 CMV	Part 1 HFPV	Part 2 HFPV	Part 3 HFPV + Surfactant
N patients	27	25	273	55
Deaths	13 (48%)	5 (20%)*	41 (15%)	6 (11%)
Survivors	14 (52%)	20 (80%)	232 (85%)	49 (89%)
Supplemental 02				
At 28d of life	6 / 14 (43%)	3 / 20 (15%)	31 / 232 (13%)	7 / 49 (14%)
At 36wks gest. age	4 / 14 (29%)	0 (0) †	8 / 232 (3%)‡	2 / 49 (4%)§

$p < 0.05$ vs CMV, † $p < 0.02$ vs CMV, ‡ $p < 0.003$ vs CMV, § $p < 0.02$ vs CMV

was no difference in HFPV patients between the three studies. Length of hospitalization among survivors was longer in study 3 versus HFPV patients in study 1. Mortality was higher in CMV patients (study 1) versus study 2 and study 3 ($p<0.001$, for both groups). Survival in study 3 is better than in study 2 and in HFPV patients in study 1 ($p<0.001$, for both).

DISCUSSION

In the first part of the study the effects of HFPV versus CMV on neonates with RDS are described. This study shows that HFPV can adequately provide oxygenation and C_{02} removal in these patients. Moreover, gas exchange is superior with HFPV compared to CMV as suggested by the increased values for P_{a02}/ F_{I02} as early as 1 hour of mechanical ventilation, and the decrease in P_{aC02} after 6 hours (figure 3). Furthermore, these differences were achieved at lower ventilatory pressures (figure 4). This difference in mean P_{aw} is not related to a difference in RDS severity between the two groups, but rather reflects the possibility of percussive ventilation to adequately ventilate patients at low airway pressures. Similar observations have been reported in infants with HMD.[17] In this study, patients were switched from CMV to HFPV, which resulted in a dramatic improvement in gas exchange. Ventilation was also improved, with a significant decrease in P_{aC02} without hemodynamic changes. Return to CMV was associated with a fall in oxygenation index. Clinical trials comparing HFPV with CMV in the treatment of adult and pediatric patients with acute respiratory failure, such as burn with smoke inhalation, trauma and ARDS, have demonstrated the ability of HFPV to improve gas exchange, reduce pulmonary morbidity and mortality.[24-29] The improvement in oxygenation and gas exchange during HFPV appears generally to coincide with overall pulmonary recruitment. However, recruitment may not be the only mechanism involved in the improved oxygenation, which was engendered with lower mean P_{aw} when compared to CMV. We hypothesized that there are other mechanisms (factors) affecting gas transport during HFPV. They are:

1. According to Newton's third law theory *"For every action there is an equal and opposite reaction",* the percussive flow of respiratory gas into the pulmonary airways must create a cephalad counter flow. In other words, as the sub tidal volume is percussively delivered endobronchially, under high velocity, it creates a "tear drop" type penetration down the center of the airways. A backwash (reverse flow) is created along the walls of the conducting airway into the area of lower pressure, which exists behind the pulsatile displacement, creating a mechanical mixing of respiratory gases as well as a cephalad counter-flow along the walls of the airway, with spiraling flow across the bifurcational convergence zones. HFPV programming enables the clinician to select the flow amplitude, which will be automatically maintained as linear velocities within the airways are preserved. That is, as lung volumes increase, resistance to gas exchange decreases and intrapulmonary gas exchange improves.

2. During HFOV, the delivered energy through the forward stroke volume delivery into the pulmonary structures is restored with the backward mechanically created expiratory flow gradient

(potentially sub ambient). In contrast to HFOV, HFPV creates effective intrathoracic impactions by virtue of selectable pulsatile percussive energy. Consecutive percussive impactions maintain fluctuating endobronchial pressure changes, which act upon the walls of the pulmonary structures, providing for mechanical mixing while enhancing the diffusivity process of respiratory gases.

3. When we consider the intrinsic physical properties of the HFPV technique, based on the fluid clutching logic, there is an unyielding conversion from pressure to flow and flow to pressure, which automatically regulates the flow entrainment gradient across the venturi. Therefore, when restrictive and obstructed airways are recruited, pressure will drop. This result in inflow acceleration through the recruited airways the distal parenchymal pulmonary units are filled with respiratory gases.

The low incidence of CLD and barotrauma in the HFPV group can be attributed to the low mean P_{aw} during mechanical ventilation. The use of positive pressure ventilation, even for a short period, leads to significant alterations in lung parenchyma.[30] In a surfactant deficient rabbit model it was demonstrated that the damage was even worse and increased with higher peak inspiratory pressures.[31] Several authors established that the early use of HFV can prevent edema and development of hyaline membrane formation, improve gas exchange and decrease the incidence of air leak in animal models.[32-34] In adult baboons, and recently also in children with smoke-inhalation injury, the use of HFPV resulted in significantly less histopathological parenchymal damage and leads to a decrease in ventilator-induced lung injury when compared to HFOV[35] and CMV.[35,36] Our results show that the incidence of CLD is lower with HFPV compared to CMV (table 3). This may be related to the fact that neonates, assigned to HFPV, were immediately and exclusively ventilated with this technique. These data are in agreement with the findings of several randomized trials, which demonstrate that HFV, as the first and predominant mode of ventilatory support, decreases the incidence of CLD in infants with RDS.[10,11,37] Some trials have reported an increase in air leak with HFV, whereas others showed no difference with CMV.[9,38,39] Two recent Cochrane Reviews mention that the use of elective HFOV and HFJV improves pulmonary outcome in preterm infants with RDS. However, mortality is not reduced when compared to CMV. Furthermore, HFJV may be associated with an increase in acute brain injury.[40,41]

Our patients in the HFPV group had a lower incidence of pulmonary air leak compared with the CMV group. For more than three decades, we have known that even in the normal lung we face a problem of preferential airway, described as interregional inhomogeneities of end-expiratory lung volume, airway opening and closing pressures and distribution of gas-flow into the airways. Moreover, we know that an applied static or quasistatic airway pressure will inevitably increase regional end-expiratory alveolar volume. With classical ventilation, it is evident that when pulmonary structure dysfunction increases, it becomes impossible to keep dependent alveoli above their closing pressures without reaching potentially damaging PIP, even with permissive hypercapnia protocols.[42]

In premature infants with hyaline membrane disease, HFPV can provide similar oxygenation and C_{02} elimination at equal mean lung volumes compared to CMV, but at lower mean alveolar pressures, suggesting that the inspiration waveform of HFPV reduces the risk of pulmonary air leak.[43] Another publication also suggests that HFPV may have a favorable effect on gas exchange and on the progression of lung disease, such as pulmonary interstitial emphysema, even when used as salvage therapy.[18]

The origin of IVH in premature infants is multifactorial and has been associated with hypoxia, hypotension, acidosis and hypocarbia. Some studies associate an increase of IVH with the use of HFV, whereas other studies report no difference.[12,44,45] High intrathoracic pressures during mechanical ventilation and decreased venous return may account for an increased risk in IVH. In our patients, venous return and intracranial pressure may well be less influenced in the HFPV group due to the lower airway pressures. This may explain the lower incidence of IVH in these patients. The lower incidence of air leak, IVH, CLD and the higher number of ventilation free days in the HFPV group reflects the potential for HFPV as a protective ventilation technique. The ability to maintain adequate gas exchange with lower

airway pressures and the rapidly declining need for inspired oxygen concentrations may account for the difference in air leak and CLD between the two groups. This may also explain the difference in duration

of mechanical ventilation and length of hospitalization. Moreover, the high incidence in IVH and air leak in the CMV group probably contributes to the difference in mortality between both groups.

The retrospective analysis in part 2 and 3 of this study, supports the results of our prospective randomized trial, and shows a lower incidence in air leak, CLD, duration of ventilation and mortality in group 2 and 3 versus CMV patients in group 1, despite the difference in birth weight, the decrease in gestational age (group 2 and 3) and the age at intubation (group 3) over the course of the studies. The longer duration of hospitalization in group 3 versus HFPV treated patients in group 1 probably reflects the difference in study population. Despite these differences, mortality in group 3 is lower than in group 1 (both CMV and HFPV) and group 2. The retrospective nature of our study does not allow to explain these differences. Therapeutic advances in neonatology that includes the use of maternal steroid administration to enhance fetal lung maturation, exogenous surfactant administration and early implementation of nasal continuous positive airway pressure to achieve stable aerated pulmonary structures, may all have contributed to the improved outcome. Also, the rate of IVH, air leak and CLD in group 3 is comparable to data from recent multicenter studies, comparing CMV to HFOV.[13,14]

Also surfactant was not used in the prospective randomized trial (part 1) that dates back to the second half of the eighties, when surfactant was not available. In fact both groups (CMV and HFPV, respectively) did not receive surfactant. We can not exclude that the use of surfactant might have resulted in a smaller difference in outcome between the two groups. However, the mortality and incidence of adverse pulmonary outcomes in the HFPV group is much lower than nowadays reported in this patient population submitted to CMV and surfactant treatment. The incidence of CLD is reported to be 26%[46] and the mortality rates when using a protective ventilation strategy varies between 17 and 34 %.[13] Although the mortality rate in our CMV group (part 1) was high 48%, it is comparable to the rate of 40% reported by authors at that time.[47] Since the mortality rate (20%) and pulmonary outcome in our HFPV group (part 1) were significantly lower than CMV, we decided to use HFPV in all newborn patients requiring mechanical ventilation for RDS. Despite encouraging results of our studies, we acknowledge that understanding of HFPV principles are essential to maximally profit of its potential advantages. Indeed, sometimes, it is easier to bring a new device into a unit than to change the mindset of the people using it.

We conclude that HFPV is a protective ventilation technique that can be used safely in neonates with RDS. Our study design does not permit us to foresee a clear advantage of HFPV over contemporary CMV or other HFV techniques. However, since HFPV can adequately provide gas exchange with a relatively low inspiratory oxygen fraction and low airway pressures, combined with a low incidence of air leak, IVH and CLD compared to recent data. Despite that, HFPV ventilators are widely available and have an increasing body of basic and clinical literature and increasing proponents, a prospective trial should be initiated in order to investigate whether this ventilation technique could further improve morbidity and mortality in neonates with respiratory distress syndrome compared to other contemporary ventilation techniques.

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