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

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 (FI\textsubscript{O}\textsubscript{2}) of > 0.30, so they were intubated. 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\textsubscript{DP}) 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\textsubscript{DP} 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 Fi\textsubscript{O}\textsubscript{2} was weaned to keep normoxemia (Pa\textsubscript{O}\textsubscript{2}, 55–80 mmHg).

The patients were weaned to nasal CPAP (nCPAP) when the following criteria were fulfilled: (1) PA\textsubscript{DP} ≤ 6.5 cm\textsubscript{O} and Fi\textsubscript{O}\textsubscript{2} ≤ 0.30 and (2) the patient started to breathe spontaneously and good breath sounds could be heard during spontaneous breathing.