Eur J Pediatr (2003) 162: 219–226
DOI 10.1007/s00431-002-1145-z

ORIGINAL PAPER

Patrick Van Reempts · Christel Borstlap
Sabine Laroche · Jean-Claude Van der Auwera

Early use of high frequency ventilation in the premature neonate

Received: 2 August 2002 / Revised: 8 November 2002 / Accepted: 25 November 2002 / Published online: 4 February 2003

Abstract This study evaluated whether the early use of high frequency ventilation (HFV) decreased the incidence of oxygen dependency at 36 weeks postconceptual age [chronic lung disease (CLD)] and improved developmental outcome. Neonates of less than 32 weeks gestational age needing ventilatory support for RDS who were admitted to a tertiary academic neonatal intensive care unit (NICU) within 6 h of birth were included in a prospective controlled clinical trial. With randomisation they were given either HFV ($n = 147$) or conventional ventilation (CV) ($n = 153$). As a primary outcome variable, ventilator and/or oxygen dependence at a postconceptual age of 36 weeks (CLD) was measured. Secondary outcome variables were: mortality at discharge, treatment failure, ventilator and/or oxygen dependence at 28–30 days (bronchopulmonary disease [BPD]), duration of ventilation, use of surfactant, days in oxygen and on continuous positive airway pressure (CPAP), survival without BPD or CLD, air leak, intracranial haemorrhages (ICH) grades 3 and 4, periventricular leukomalacia (PVL) grades 1 and 2, retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), necrotising enterocolitis (NEC), developmental outcome at 7 to 12 months and if necessary at 18–24 months corrected age. The results showed that CLD (16.3 vs. 12.4%), BPD (33.3 vs. 36.6%), early cerebral abnormalities, mortality at discharge (17.2 vs. 13.2%), failure rate (11.6 vs. 6.5%) and motor and mental developmental outcome at a corrected age of 18 to 24 months ($p > 0.05$) did not differ between the two groups. *Conclusion*: Under the present study design HFV compared with CV did not decrease chronic lung disease and no developmental outcome differences could be found at a corrected age of almost 2 years.

Keywords Neonatal intensive care · Prematurity · High frequency ventilation · Chronic lung disease · Developmental outcome

Abbreviations *BPD* bronchopulmonary disease · *BW* birth weight · *CDD* Centre for Developmental Disorders · *CLD* chronic lung disease · *CV* conventional ventilation · *GA* gestational age · *HFV* high frequency ventilation · *HVS* high volume strategy · *ICH* intracranial haemorrhage · *IUGR* intrauterine growth retardation · *MAP* mean airway pressure · *MDI* Bayley Motor Developmental Index · *NEC* necrotising enterocolitis · *NICU* neonatal intensive care unit · *PCA* postconceptual age · *PDA* patent ductus arteriosus · *PEEP* peak end-expiratory pressure · *PIE* pulmonary interstitial emphysema · *PIP* peak inspiratory pressure · *PPROM* premature prolonged rupture of the membranes · *RDS* respiratory distress syndrome · *ROP* retinopathy of prematurity

Introduction

Prenatal maternal corticoid administration and/or postnatal surfactant administration, oxygen treatment and respiratory support, mainly conventional ventilation (CV), are still the mainstays of the prevention and treatment of respiratory distress syndrome (RDS). Despite improvement in CV, 25% of neonates with a birth weight between 500 and 1,000 g are oxygen dependent at 36 weeks' postconceptual age [38]. High frequency ventilation (HFV) has been shown to improve gas exchange, reduce lung injury, decrease the length of ventilatory support, to be more effective when used early and to restrict the incidence of chronic lung disease (CLD) in comparison to CV [2, 3, 7, 19, 20, 27, 28, 34, 36, 42]. However, there still exists controversy: the HIFI trial,

P. Van Reempts (✉) · C. Borstlap · S. Laroche
Department of Paediatrics, Division of Neonatology,
University Hospital Antwerp, Wilrijkstraat 10,
2650 Antwerp (Edegem), Belgium
E-mail: Patrick.Van.Reempts@uza.be
Tel.: +32-3-8215802
Fax: +32-3-8214802

J.-C. Van der Auwera
Department of Epidemiology and Social Medicine,
University of Antwerp, Antwerp, Belgium

recent studies, reviews and the Cochrane systematic meta-analysis do not support the routine use of HFV in preterm neonates [6, 12, 13, 14, 41, 42]. Also, until recently many trials suffered from the absence of prenatal corticoid or postnatal surfactant administration, late introduction of HFV, did not pursue CV strategies that attempted to minimise volutrauma or suffered from a lack of power [2, 8, 30, 34, 35, 41]. Furthermore, in studies not using a high volume strategy (HVS) [14, 35], or recently in those that did use a HVS [29], short-term neurodevelopmental outcome seems less favourable in the HFV group, with an increase in grade 3–4 intracranial haemorrhage (ICH) and in periventricular leukomalacia (PVL). Moreover, few studies have reported on long-term developmental outcome and only one study found no difference in pulmonary outcome at the age of 8–9 years [13, 32]. In view of these limitations we hypothesised that by using an appropriate conventional ventilatory strategy with high rates and fairly low peak inspiratory pressures (PIP), and by not specifically aiming for an aggressive HVS, but rather sufficient oxygenation, the respiratory and also the developmental outcome would be similar for the two modes of ventilation. In the present, prospectively randomised, controlled clinical trial we thus report our experience in terms of morbidity before discharge, mortality and moderate long-term neurodevelopmental outcome, comparing HFV with CV in neonates <32 weeks gestational age (GA) who were admitted to a single neonatal intensive care unit (NICU) within 6 h of birth.

Materials and methods

Study population

Infants of less than 32 weeks' gestational age, admitted within 6 h of birth to a NICU were eligible for randomisation if they fulfilled the following criteria: need for intubation, FiO_2 need >0.40 or a mean airway pressure (MAP)$\times FiO_2 > 3.8$, using the initial settings as outlined below, and a chest X-ray suggestive of RDS. Infants were excluded from randomisation if they showed clinically obvious major congenital anomalies or active infection at birth. They were randomised in the neonatal unit using sealed folded papers and given either HFV or CV.

Respiratory care

HFV was provided by a Sensor Medics 3100A oscillator (Sensor Medics BV Bilthoven, the Netherlands). If a Sensor Medics 3100A oscillator was not available an Infant Star (I.S. Infrasonics, Nellcor Puritan Benett, San Diego, CA, USA) was used. The latter is a high frequency flow interrupter with an active expiratory phase. Randomised infants were started on a MAP of 8 cm H_2O for infants <29 weeks and 10 cm H_2O for neonates 29–31 6/7 GA with FiO_2 as needed. This was to prevent possible overdistention [33]. When oxygen saturation dropped $<88\%$ MAP was increased by 1–2 cm H_2O every 10–15 min until oxygenation improved to above 94%, but less than 95% (upper limit) Then FiO_2 was decreased stepwise if possible. It was expected that a stable FiO_2 could be reached within 60–120 min of initiating HFV [9]. A chest radiograph was performed to check for overinflation (>9 posterior ribs and flattening of the diaphragm). If there was overinflation the MAP was reduced by 0.5–1 cm H_2O while still aiming for oxygen saturation above 94%. Blood pressure optimisation with dopamine and volume support was used as necessary. The pressure amplitude (delta P) was set at a value that produced visible chest wall movement. Neonates were monitored preferentially using an umbilical arterial or a preductal peripheral arterial line. Most also had transcutaneous PO_2 and PCO_2 monitoring. The target postductal $PaCO_2$ was initially between 35 and 45 mmHg and later a $PaCO_2$ of up to 70 mmHg was allowed, while pH was kept between 7.25–7.45. If ventilation needed to be improved the delta P was increased. The frequency was set at 10 Hz.

For CV pressure-limited, time-cycled ventilators (Infant Star, Nellcor Puritan Benett Inc, Carlsbad, CA; Babylog 8000, Dräger Medizin-technik, Lübeck, Germany) were used. Initial settings were a peak inspiratory pressure (PIP) of 20 cm H_20 and end-expiratory pressure (PEEP) of 4 cm H_2O, a rate of 80 breaths per minute, inspiratory to expiratory ratio of 1:1.1 with an inspiratory time <0.35 s and a flow of 8 l/min. Further ventilatory changes were made according to the clinical judgement of the attending neonatologist. Overall intermittent positive pressure ventilation using high rates and a relatively low PIP were used, as reported recently [41]. In short, we recommended that if FiO_2 was >0.40 end-expiratory pressure was increased by 1–2 cm H_2O until oxygenation improved or there were signs of decreased cardiac output, or until the chest radiograph showed normal inflation. The maximum PEEP for neonates of <29 weeks GA was 6 cm H_2O and 8 cm H_2O for neonates of 29–31 weeks GA. If there was overinflation the PEEP was reduced by 1–2 cm H_2O until oxygenation improved. If there was poor cardiac performance, characterised by low mean blood pressure (<30 mmHg) and hypoxaemia, optimisation of vasopressor and volume support was aimed for. In terms of ventilation, a PIP that produced good chest wall movement was aimed for with a rate and PEEP similar to those achieved during the stabilisation period. In case of hypercarbia the rate was increased when the patient had good lung inflation on chest radiograph and a good tidal volume delivery based on good chest wall movement or a tidal volume measurement of 6–8 ml/kg, or when a PIP of 25 cm H_2O had been reached for neonates of <29 weeks GA or 30 cm H_2O for neonates of 29–31 weeks GA. Hypercarbia was managed by increasing the peak inspiratory pressure when lung inflation was inadequate despite optimal or maximal end expiratory pressure, or when the rate was >80/min. In patients with hypercarbia and lung hyperinflation, the end expiratory pressure was reduced in order to improve ventilation. The final strategy was to use relatively high rates with a PIP that produced PCO_2 of between 35 and 45 during the acute phase and up to 70 mmHg later.

After initial respiratory stabilisation either on CV or on HFV, neonates were given surfactant (Alveofact, Boehringer Ingelheim Pharma, Biberach an der Riss, Germany, or Survanta, Abbott Laboratories, Brussels, Belgium) in a dose of 100 mg/kg, if $FiO_2 > 0.40$ ($FiO_2 > 0.30$ if GA <27 weeks). If possible the trachea was not aspirated (in-line suction) (Ballard TRACHCARE, Ballard Medical products, Draper, UT, USA) for 6 h. The second dose of surfactant was given not earlier than 2 h after the first dose. The third and fourth doses were given after an interval of 6 h after the previous dose. A maximum of four doses were given. The neonates on HFV were preferentially extubated directly from HFV. For neonates <29 weeks this was at a FiO_2 of $<30\%$ and a MAP of <6 cm H_2O. For neonates 29–31 weeks GA this could be at a FiO_2 of $<30\%$ and a MAP of <8 cm H_2O. Delta pressure was decreased until chest wall movements were not visible. Weaning failure was defined as an inability to decrease the FiO_2 by 5% or the inability to decrease the MAP by more than 1 cm H_2O over 3 weeks for neonates of <29 weeks GA, over 2 weeks for neonates of 29–31 weeks GA. If this failed the patient was moved to CV. After extubation neonates of <29 weeks GA were moved to nasal or nasopharyngeal continuous positive airway pressure (CPAP), neonates of 29–31 weeks GA were preferentially put under a head box. In the CV weaning process, PIP was decreased preferentially below 18 cmH_2O for neonates with a GA of <29 weeks, and below 20 cmH_2O for GA of 29–31 weeks. If pH remained above 7.32 and PCO_2 below

55 mmHg the respiratory rate was decreased in decrements of 5. Infants with a GA of >29 weeks and those with a GA of <28 weeks were extubated at a respiratory rate of 10/min and 5/min respectively and put under a head box with oxygen, or if this failed nasal or nasopharyngeal CPAP (5 cmH_2O) was instituted. Before extubation caffeine citrate therapy was started in both groups. If the neonate was not extubated by day 7 of life, fluids were restricted to 120–130 ml/kg/day (including medication) with a caloric intake of >80 cal/kg/day and a sodium intake of 3 to 4 meq/kg/day. If still on the ventilator on day 10 diuretics were started: soldactone 2×1 mg/kg/day IV and furosemide 2×1 mg/kg/day IV or aldactone 2×1 mg/kg/day and esidrex 2×2 mg/kg/day if administered orally. Also on day 10 infectious parameters (CRP, blood and urine cultures) were checked and if negative on day 13 dexamethasone was started: IV or per os at 0.5 mg/kg/day × 3 days, followed by 0.25 mg/kg/day for 3 days and finally 0.1 mg/kg/day for 3 days. An ultrasound scan of the brain (Sonos 1500 imaging system, Hewlett-Packard, Andover, MA, USA, 7.5 MHz transducer) was carried out on days 1, 2 and 3, and weekly thereafter or as clinically indicated. Grading of ICH and PVL was performed according to Papile et al., Shankaran et al. and de Vries et al. [8, 31, 37] and retinopathy of prematurity (ROP) according to the international classification of retinopathy of prematurity [4]. Decisions regarding grading for BPD or CLD, ICH, leukomalacia and ROP were performed by professionals not familiar with the treatment protocol.

Treatment failure

Treatment failure was defined as:

1. Failure within the first 7 days of life to maintain for more than 2 h a PaO_2 of more than 50 mmHg or an arterial oxygen saturation of more than 85% on a FiO_2 of 1, or to decrease PCO_2 below 70 mmHg, or to decrease MAP to <20 if GA was <29 weeks or MAP to <25 if GA was 29–31 weeks on HFV, or to decrease PIP to <30 if GA was <29 weeks or PIP to <35 if GA was 29–31 weeks on CV
2. Uncontrollable air leak
3. Cardiovascular dysfunction (uncontrollable hypotension, cardiogenic shock)
4. Need for hand ventilation to maintain adequate gas exchange.

The neonate was then changed to the other ventilatory mode.

General infant care and long-term evaluation

Neonatal care was kept similar for the HFV and CV group till the postconceptual age of 36 weeks or until discharge from the neonatal unit, whichever came first.

Only infants with a GA of <30 weeks or a BW of $<1{,}250$ g or neonates with intracranial lesions were included in the follow-up program of the Centre for Developmental Disorders (CDD) ($n=138$). These infants were evaluated between 7 and 12 months post-term age. If abnormal a new examination was planned at the post-term age of between 18 and 24 months. The following parameters were assessed: MDI (Bayley Motor Developmental Index, MotorDI), neuromotor development (normal: absence of mono-, di-, para-, or quadriplegia, absence of any muscle tone abnormalities, absence of visual or hearing impairments; or abnormal) and cognitive performance (Bayley Mental Developmental Index, MentDI).

Data monitoring

The following data were collected:

- Maternal: vaginal bleeding, maternal hypertension, including preeclampsia, prolonged rupture of membranes, chorioamnionitis, use of tocolytics, lung maturation with corticoids
- Neonatal: total days of HFV and/or CV and/or CPAP, total days on supplemental oxygen, doses of surfactant

The following parameters were registered daily for the first 7 days of life and when applicable: the mean of PIP, PEEP, FiO_2, MAP, MAP×FiO_2 (mean values were calculated as the mean of all available values over 24 h), fluid intake in cc/kg/day. The following diagnoses were recorded: intrauterine growth retardation (IUGR), asphyxia, RDS, air leak (pulmonary interstitial emphysema {PIE} [39] or pneumothorax), BPD or CLD with grading I or II according to Hyde [17] at 28 days (BPD) and 36 weeks (CLD) postconceptual age, patent ductus arteriosus (PDA) (present but not treated; present and treated with nonsteroidal anti-inflammatory drugs; present, treated medically, then ligation), necrotising enterocolitis (NEC), perinatal infection, nosocomial infection, ICH with grading 1, 2, 3 and 4, periventricular leukomalacia, surgery and ROP with grading.

Endpoints

CLD (defined as ventilator and/or oxygen dependence at a postconceptual age of 36 weeks) was chosen as the primary outcome variable. Secondary outcome variables were mortality at discharge, treatment failure, BPD (defined as ventilator and/or oxygen dependence at 28–30 days), duration of ventilation, use of surfactant, days on oxygen and on CPAP, survival without BPD or CLD, air leak, ICH grades 3 and 4, PVL grades 1 and 2, ROP, PDA, NEC, and for neonates with a birth weight of less than 1,250 g or GA of less than 30 weeks, or intracranial lesions on ultrasound developmental outcome at 7–12 months and if necessary at 18–24 months corrected age.

Sample size and statistical analysis

Based on the period prior to the present trial we calculated that between 250 and 300 ventilated neonates could be enrolled over a 3.5-year period. As the main outcome variable, CLD, was decreasing every year by 5% we aimed for a reduction of 60% at 36 weeks at the end of a 3-year recruitment period. Thus with a 95% confidence (alpha level at 0.05) and a power of 0.8 a total of at least 126 patients were needed in each group.

For qualitative and semi-qualitative data, the chi-square test or Fisher exact test was used. For continuous data one-way analysis of variance, Student's *t*-test and, when appropriate, the Mann Whitney U tests were used. Relative risk was calculated for the respiratory and nonrespiratory outcome variables. Forward stepwise multiple logistic regression was used to analyse the effect of perinatal factors (premature prolonged rupture of the membranes [PPROM], maternal hypertension, vaginal bleeding, prenatal steroids, tocolytics, mode of delivery, asphyxia, IUGR) and confounding variables (predicting worse outcome: GA, BW, duration of ventilation, PDA, fluid intake, PIE, pneumothorax, NEC, ICH 3–4) on the main outcome variables. All patients were analysed according to their initial assignment group as they were included on an intention-to-treat basis. Statistica 5.1, 1998 (Statsoft Inc., Tulsa, OK, USA) and SPSS, 1999 (version 10.01 SPSS, Chicago, IL, USA) were used for statistical analysis. The study was approved by the local Ethics Committee. Parents gave their oral consent.

Results

Between January 1997 and July 2000, 423 neonates with a GA of less than 32 weeks were admitted to the NICU: 317 were intubated and 300 were randomised and given HFV ($n=147$) or CV ($n=153$). Seventeen were not randomised due to congenital anomalies, readmission or being admitted more than 6 h after birth. Patient characteristics and perinatal data are given in Table 1.

There were no differences between the two groups. The main outcome variables, CLD at 36 weeks as well as mortality at discharge and treatment failure did not differ between the two groups (Table 2). There were 17 failures in the HFV group and 10 in the CV group ($p = 0.1$). There were also no differences in survival without BPD at 28 days or CLD at 36 weeks (Table 2). Other respiratory and nonrespiratory outcomes were similar in both groups (Tables 2, 3). None of the maternal or perinatal factors or the type of ventilation influenced BPD at 28 days or CLD at 36 weeks (data not shown).

The average number of surfactant doses was 1.2 for the HFV group and 1.1 for the CV group ($p = 0.3$). Infants treated for PDA were ventilated for a longer period, i.e. 14 ± 12 days vs. 4 ± 6 days respectively ($p < 0.001$). Untreated or treated PDA influenced the duration of ventilation, total number of days on oxygen and as such also the occurrence of BPD at 28 days, i.e. 51% vs. 25% respectively, and at 36 weeks 22% vs. 9% ($p < 0.001$). On the other hand there was no difference in the occurrence of treated PDA between the HFV and CV groups. No difference for any main outcome parameter was noted regarding inclusion time. Neonates in the HFV group were started at a median time post delivery of 56 min (range 20 min to 24 h and 55 min); in the CV group the median start time of ventilation was 53 min (range 20 min to 24 h and 51 min ($p > 0.05$). Infants intubated right after birth and assigned to either group showed similar results to those in the intention-to-treat group. In the HFV group the Sensor Medics was used for 122/147 and the Infant Star for 25/147 neonates. In the CV group the Dräger 8000 was used for 73/153 and the Infant Star for 80/153 neonates. Type of high frequency or conventional ventilator did not influence any of the outcomes (data not shown).

None of the respiratory outcome parameters differed significantly between neonates of < 29 weeks vs. > 28 weeks' GA (data not shown). Figures 1 and 2 demonstrate the evolution of FiO_2 and mean airway pressure vs. time. Also, limiting the analysis post hoc to the patients who did not fail treatment did not influence the results (data not shown). Although the total fluid intake was not different, more neonates in the HFV

Table 1 Patient characteristics and perinatal data. *HFV* high frequency ventilation, *CV* conventional ventilation, *PPROM* premature prolonged rupture ofthe membranes, *IUGR* intrauterine growth retardation, *GA* gestational age, *BW* birth weight

	HFV*n* (%)	CV*n* (%)	*P* value
Maternal hypertension	26/132 (17.7)	33/131 (25.1)	0.3
Maternal bleeding	30/132 (15.6)	39/141 (25.5)	0.8
PPROM	39/147 (26.5)	36/153 (23.5)	0.6
Tocolysis	82/135 (55.8)	76/134 (49.7)	0.6
Prenatal corticoids	71/112 (48.3)	88/134 (57.5)	0.1
Caesarean section	94/138 (63.9)	90/153 (58.8)	0.7
IUGR	17/147 (11.6)	14/153 (9.2)	0.5
Asphyxia	18/147 (12.2)	11/153 (7.2)	0.1
Anaesthesia overall			0.8
General	48/127 (32.7)	47 (130 (30.7)	
Epidural	47/127 (32)	43/130 (28.1)	
Origin overall			0.9
Inborn and IUGR	116/147 (78.9)	120/153 (78.4)	
Outborn	31/147 (21.1)	33/153 (21.6)	
GA (weeks) mean ± SD	28.5 ± 1.8	28.8 ± 1.9	0.2
BW (g) mean ± SD	$1{,}173 \pm 346$	$1{,}217 \pm 363$	0.3
Mean airway pressure (cm H_2O) mean SD	8.2 ± 1.4	8.4 ± 1.6	0.25
FiO_2 mean ± SD	0.55 ± 0.24	0.56 ± 0.25	0.72

Table 2 Main outcomes andrespiratory outcomes. *BPD* bronchopulmonary disease, chronic lung disease, *PIE* pulmonary interstitial emphysema, *CPAP* continuous positive airway pressure

	HFV ($N = 147$) *n* (%)	CV ($N = 153$) *n* (%)	*P* value	OR (CI)
Failure	17 (11.6)	10 (6.5)	0.13	1.05 (0.98–1.14)
Mortality	25 (17.2)	20 (13.2)	0.34	1.05 (0.95–1.16)
BPD 28 days	49 (33.3)	56 (36.6)	0.61	0.96 (0.81–1.13)
Survival without BPD	76 (51.7)	77 (50.3)	0.8	1.03 (0.82–1.23)
CLD 36 weeks PCA	24 (16.3)	19 (12.4)	0.33	1.05 (0.95–1.15)
Survival without CLD	98 (66.7)	114 (74.5)	0.1	0.76 (0.5–1.09)
PIE	13 (8.6)	13 (8.9)	0.9	1.04 (0.9–1.07)
Pneumothorax	11 (7.5)	7 (4.6)	0.3	1.03 (0.97–1.09)
Total days ventilation in study (mean ± SD)	6.1 ± 7.8	5.4 ± 8.5	0.5	
Mean airway pressure d1–d7 cm H_2O mean ± SD	9.7 ± 2.3	7.3 ± 1.9	0.001	
Total length ventilation (days) mean ± SD	7.7 ± 9.7	4.9 ± 9.1	0.9	
Days in oxygen > 0.21 FiO_2 (mean ± SD)	23.6 ± 28.2	22.7 ± 28.5	0.8	
Days on CPAP (mean ± SD)	7.2 ± 11.5	7.4 ± 12	0.8	
Doses of surfactant (mean ± SD)	1.2 (1.1)	1.1 (1)	0.3	

Table 3 Nonrespiratory outcome. *PDA* patent ductus arteriosus; *PDA123* not treated, treated withnonsteroidal anti-inflammatory drug (NSAID), ligated; *PDA23* treated with NSAID, ligated; *ROP* retinopathy of prematurity; *NEC* necrotising enterocolitis; *ICH* intracranial haemorrhage

	HFV ($N=147$) *n* (%)	CV ($N=153$) *n* (%)	*P* value	OR (CI)
ICH all grades	39 (26.9)	28 (18.3)	0.9	1.1 (0.98–1.26)
ICH grade 1 or 2	30 (20.4)	25 (16.3)	0.4	1.05 (0.94–1.17)
ICH grade 3 or 4	14 (9.5)	13 (8.5)	0.8	1.01 (0.94–1.09)
PVL	11 (7.5)	8 (5.3)	0.6	1.02 (0.96–1.09)
ROP	8 (7.5)	10 (9.8)	0.8	1.01 (0.85–1.21)
RP grade 3 and 4	2 (1.3)	1 (0.7)	0.6	0.99 (0.97–11.02)
PDA 123	56 (38.1)	57 (37.3)	0.8	1.04 (0.65–1.65)
PDA 23	42 (28.6)	32 (20.9)	0.1	1.1 (0.97–1.26)
NEC	10 (6.8)	14 (9.2)	0.4	0.98 (0.91–1.04)
Sepsis proven and suspected	35 (23.8)	43 (28.2)	0.5	0.95 (0.83–1.08)
Sepsis proven	19 (12.9)	20 (13.1)	0.9	0.9 (0.91–1.09)

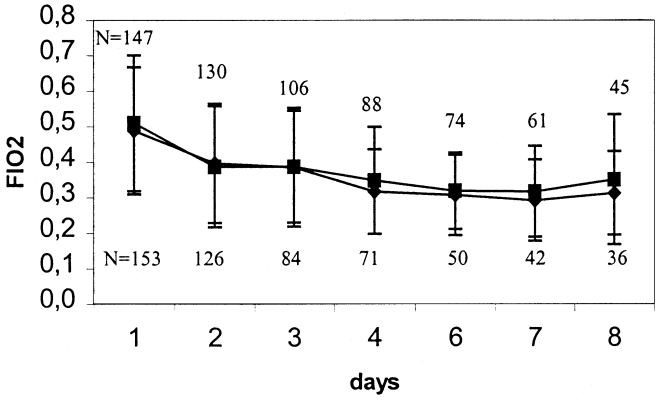

Fig. 1 Time course of FIO2 represented as mean ± SD for the HFV group (*squares*) and CV group (*diamonds*). $P>0.05$ on all days. *Numbers below and above graphs* indicate *n*-values in HFV and CV group

group received vasopressor support (HFV: 72/147 vs. CV: 49/153) ($p<0.05$).

In the follow-up program the 138 neonates (HFV: $n=70$ and CV: $n=68$) were assessed at the corrected age of 7–12 months. For these infants the Bayley Motor Developmental Index, the Mental Developmental Index, the motor diagnosis, the neuromotor diagnosis and the cognitive assessment did not differ between the two groups (all $p>0.05$) (Table 4). Forty-two (60%) infants in the HFV and 48 (70%) infants in the CV group were considered to be completely normal. Also, in a subgroup analysis for 26 neonates in the HFV group and 25 neonates in the CV group no differences were found. None of the HFV but 4 of the CV group showed abnormalities at the 18–24 months corrected age assessment.

Discussion

In this randomised clinical trial early use of HFV did not reduce CLD at 36 weeks postconceptual age, BPD at 28 days, failure rate or mortality before discharge when compared with CV. In the follow-up period up to a corrected age of 18 to 24 months no developmental outcome differences could be found.

Thus our results suggest that in our population either mode of ventilation was equally adequate for use in the premature neonate.

There are limitations to the present study. First, some neonates were randomised later than the 6-h inclusion period after birth but were included in the analysis, since

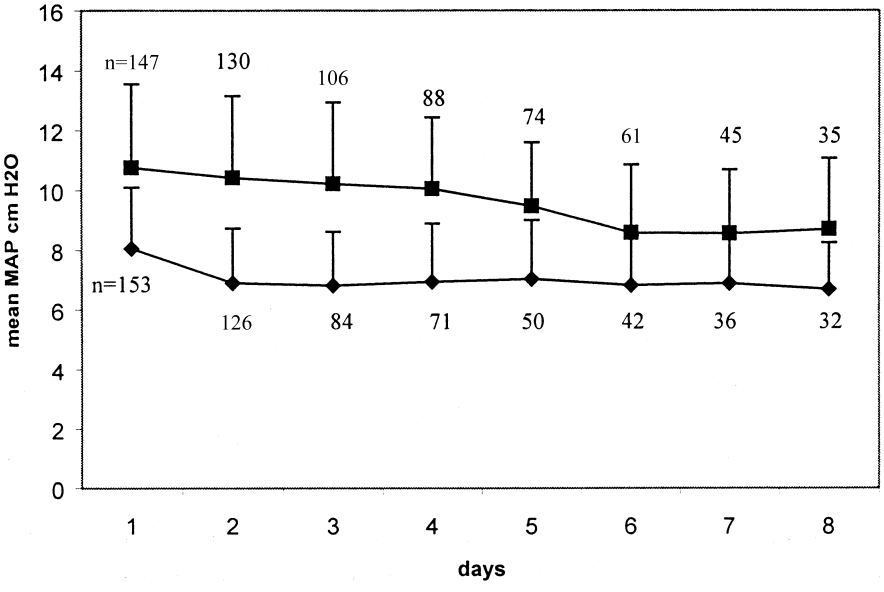

Fig. 2 Time course of mean airway pressure and represented as mean ± SD for the HFV group (*squares*) and CV group (*diamonds*). $P<0.05$ on all days. *Numbers below and above graphs* indicate *n*-values in HFV and CV group

Table 4 Developmental outcome

	HFV ($n=70$)	CV ($n=68$)	P value
GA (weeks) mean ± SD	28.6 ± 1.5	28.7 ± 1.6	0.6
BW (g) mean ± SD	1,210 ± 302	1,216 ± 308	0.9
Motor developmental index			
Mean ± SD	97.5 ± 21	97 ± 21	0.9
Number of infants with MDI > = 80 (%)	64 (92)	60 (88)	
Number of infants with MDI < 80 (%)	6 (8)	8 (12)	
Motor diagnosis			0.4
Number of infants normal (%)	45 (65)	49 (72)	
Number of infants abnormal (%)	24 (35)	19 (28)	
Neuromotor diagnosis			0.1
Number of infants normal (%)	60 (85)	64 (94)	
Number of infants abnormal (%)	10 (15)	4 (6)	
Mental developmental index			0.7
Mean ± SD	106 ± 17.1	107.3 ± 22.8	
Number of infants with MDI > = 80 (%)	65 (93)	62 (91)	
Number of infants with MDI < 80 (%)	5 (7)	6 (9)	
Cognitive development			0.9
Number of infants normal (%)	60 (85)	60 (89)	
Number of infants abnormal (%)	10 (15)	8 (11)	

the study was based on an intention-to-treat protocol. Therefore, it is possible that lung injury had already occurred during resuscitation at birth or during transport with conventional ventilation for admission to the neonatal unit. Early application of HFV with a HVS after birth could be one of the most important factors in preventing and reducing CLD [21, 22, 26]. In our study, ventilation was started at a median time of 55 and 53 min after birth for HFV and CV, respectively. Transporting a neonate on CV and starting HFV on admission to the unit, however, does not seem to cause any major problems [25]. Since the time of treatment allocation and the criteria for needing intubation and ventilation did not differ between the groups we feel confident that intubation and randomisation some time after birth did not obscure our results. Moreover, when focusing on the group of infants intubated right after birth and assigned to either group, analysis of the outcome variables showed similar results to the intention-to-treat group. Second, although we did not use an aggressive high volume strategy, MAP always remained significantly higher for the HFV group, as can be deduced from Fig. 2, and is very similar to the MAPs reached in recent studies [6, 12]. It is still not clear whether a HVS vs. an optimal volume is needed as most studies have focused on the beneficial effect of HFV on respiratory morbidity without really examining the effects of a more optimal conventional ventilatory strategy. This is supported by a study in animals demonstrating that pressure controlled ventilation with a sufficient level of positive end-expiratory pressure and small driving pressure amplitudes was as effective as high frequency oscillatory ventilation at maintaining optimal gas exchange and improving lung mechanics [44]. Third, the developmental follow-up did not include all surviving infants due to subsidy restrictions, but only those with a GA of < 30 weeks or a BW of < 1,250 g or neonates with intracranial lesions. This does not put our results at a disadvantage since the most critical group was assessed. Our findings of similar short-term respiratory and neurological outcomes for HFV and CV are in agreement with a Cochrane analysis and a review by Thome and Carlo, which were not able to conclude that HFV was superior to CV [13, 40]. However there seemed to be a decrease in CLD and BPD or death, especially in the smaller studies in which a high volume strategy (HVS) was used, but there was an increase in IVH grades 3 or 4 and PVL and an increase in air leaks in the larger studies. The HIFI trial, using a low volume strategy, always had a major impact on the results of these meta-analyses [13, 40]. Although, Rettwitz, intentionally using a less aggressive lung volume strategy, as we did, was also not able to demonstrate differences in mortality and morbidity. None of the infants had CLD but the study population did not include infants of < 750 g birth weight [35]. The recent French multicentre study using HVS in neonates of < 30 weeks, reported less use of surfactant in the HFV group, no difference in oxygen dependency at 28 days, a trend toward less CLD, but more frequent and severe ICH in the HFV group [29]. This is in contrast to our findings demonstrating no difference in surfactant use, CLD and BPD, but also no increase in grades 3 or 4 ICH, although our population was somewhat less premature. On the other hand, a retrospective analysis by Rimensberger, using HFV as a first intention-to-treat option demonstrated less CLD in the HFV group compared with the CV group (0% vs. 34%) [36]. It is not clear from the latter study which criteria were used for intubation and ensuing ventilation, and whether CPAP could have been a valid initial alternative. Preliminary results from a large trial, enrolling 500 neonates between 601 to 1,200 g showed earlier extubation in the HFV group (17.4 ± 16.6 vs. 24.2 ± 19.2 days for the CV group) as well as more infants alive and free of respiratory support at a corrected age of 36 weeks (57% vs. 47%) [7]. Although these infants were smaller than in our group, it seems that our CV group, using rather high respiratory rates,

moderate PIP and rather liberal CO2 were ventilated for a shorter time (mean of 4.9 days), which is also shorter than has been reported in most HFV trials. This may explain why in some recent studies, as in our study, HFV was no more beneficial than CV [29, 34, 36, 41]. Our results are further supported by the findings of the UK Oscillation Study performed in about 800 infants with a GA of <29 weeks and using different devices. This study also showed that early use of HFV did not reduce the incidence of CLD and that HFV did not increase the risk of major cerebral abnormality [23].

However, contrast remains with animal studies, showing an advantage of HFV over CV [27, 28]. These studies have been carried out under ideal conditions, i.e. every step in the high frequency care of the animal was refined so that in the ideal situation the animal was put on high frequency ventilation right after delivery with very low risk of exposure to high tidal volumes. This attitude may have avoided the initial shear stress, with less risk of lung inflammation and thus less risk of BPD [1, 11]. Although sustained lung inflation, better pulmonary mechanics and less inflammation have been demonstrated in the premature baboon ventilated for 28 days with HFV, enhanced alveolisation, critical in the development of BPD, was not observed [45]. One group, however, could not find differences in inflammatory mediators in the tracheal aspirate collected during the first 10 days of life of IPPV or HFV infants randomised within 1 h of intubation [40]. On the other hand, there now is evidence that some modes of HFV may cause trauma. At low lung compliance the high frequency oscillatory pressure waveform from the airway opening to the lung alveoli may be greater than previously considered. Also, the actual pressure amplitudes superimposed on possibly high PEEP or MAP during HFV may generate barotrauma instead of volutrauma [33]. The fact that we did not need to use a very high MAP, probably somewhat less than reported, may explain why we did not find more air leaks, CLD or BPD: all considered to at least partly result from ventilator injury [9, 33]. Thus it seems that the therapeutic window for HFV is narrow, and close monitoring and experience remain a prerequisite to its success [9].

Long term pulmonary outcome as reported in the literature has not yet shown major differences between HFV and CV [16, 30, 32].

Although we need to be cautious since our follow-up was not complete, we were not able to show developmental differences at a corrected age of almost 2 years. Knowing, however, that our data covered the highest risk group with a gestational age of below 30 weeks, this is certainly reassuring. Few authors have reported long-term neurodevelopmental outcome [5, 10, 13]. Ogawa reported an incidence of 9% developmental delay in both groups at 12 months of age, whereas the HIFI study reported a lower incidence of normal developmental outcome in the HFV vs. the CV group at a corrected age of between 16 and 24 months [15, 30]. A subgroup of 23 infants in the HIFI trial who were assessed at the age of 6–7 years, and published so far only in abstract form, did not reveal cognitive differences between HFV and CV groups [18]. Neither was there a difference in developmental outcome between HFV and CV at 6.4 years in a subgroup of the PROVO trial [10]. One study reported a trend towards less ROP. We were not able to show this and a longer follow-up is probably necessary [41].

In conclusion, we were not able to demonstrate a superiority of HFV over CV as expressed by CLD, BPD and other respiratory and nonrespiratory parameters, and there were no differences in developmental outcome at a corrected age between 18 and 24 months. The therapeutic window for HFV is narrow and thus also the risk-benefit ratio [9]. In view of our findings it therefore seems reasonable to suggest that further studies should concentrate not only on how HFV is practised but also on CV strategies using relatively low PIP and rapid ventilatory rates as we did or using new CV modes such as volume guarantee and pressure support. However, neither our data nor the current literature currently point to a superior long-term effect of HFV [24, 43].

References

1. Carlton DP, Albertine KH, Ribeiro SP, Cho SC, Lont M, Bland RD (1997) Role of neutrophils in lung vascular injury and oedema after premature birth in lambs. J Appl Physiol 83:1307–1317
2. Clark RH (1994) High-frequency ventilation. J Pediatr 5:661–670
3. 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
4. Committee for the Classification of Retinopathy of Prematurity. (1984) An international classification of retinopathy of prematurity. Arch Ophthalmol 102:1130–1134
5. Cools F, Offringa M (1999) Meta-analysis of elective high frequency ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 80:F15–20
6. Courtney SE, Weber KR, Spohn WA, Bender CV, Malin SW, Gotshall RW (1992) Cardiorespiratory effects of changing inspiratory to expiratory ratio during high-frequency oscillation in an animal model of respiratory failure. Pediatr Pulmonol 13:113–116
7. Courtney SE, Durand DJ, Asselin JM et al (2001) Early high frequency ventilation versus synchronized intermittent mandatory ventilation in very low birth weight infants. Pediatr Res 49:387A
8. De Vries LS, Eken P, Dubowitz LM (1992) The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 49:1–6
9. 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
10. Gerstmann DR, Wood K, Miller A, Steffen M, Ogden B, Stoddard RA, Minton SD (2001) Childhood outcome after early high-frequency oscillatory ventilation for neonatal respiratory distress syndrome. Pediatrics 108:617–623
11. Groneck P, Speer CP (1995) Inflammatory mediators and bronchopulmonary dysplasia. Arch Dis Child 73:F1–F3

12. Halliday HL (2002) Early postnatal dexamethasone and cerebral palsy. Pediatrics 109:1168–1169
13. Henderson-Smart DJ, Bhuta T, Cools F, Offringa M (2001) Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev CD000104
14. HIFI Study Group (1989) High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. The HIFI Study Group. N Engl J Med 320:88–93
15. HIFI Study Group (1990) High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. HiFi Study Group. J Pediatr 116:933–941
16. HIFI Study Group (1990) High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. The HIFI Study Group. J Pediatr 117:939–946
17. Hyde I, English RE, Williams JD (1989) The changing pattern of chronic lung disease of prematurity. Arch Dis Child 64:448–451
18. Inwood S, Frisk VA, Kelly EN (1998) High-frequency oscillation vs conventional mechanical ventilation: cognitive abilities at school age. Pediatr Res 4:A1271
19. Jackson JC, Truog WE, Standaert TA, Juul SE, Murphy JH, Chi EY, Mackenzie AP, Hodson WA (1991) Effect of high-frequency ventilation on the development of alveolar edema in premature monkeys at risk for hyaline membrane disease. Am Rev Respir Dis 143:865–871
20. 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
21. Jobe AH (1998) Too many unvalidated new therapies to prevent chronic lung disease in preterm infants. J Pediatr 132:200–202
22. Jobe AH, Ikegami M (1998) Mechanisms initiating lung injury in the preterm. Early Hum Dev 53:81–94
23. Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L, Calvert SA, the United Kingdom Oscillation Study Group (2002) High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 347:633–642
24. Keszler M, Durand DJ (2001) Neonatal high-frequency ventilation. Past, present, and future. Clin Perinatol 28:579–607
25. Mannix PA, Costeloe K, Roper J (1996) High frequency ventilation is a feasible method of ventilation from admission in the very preterm infant [abstract G65]. In: Proceedings of the British Paediatric Association Annual Meeting, p 54
26. Marlow N (1998) High frequency ventilation and respiratory distress syndrome: do we have an answer? Arch Dis Child 78:F1–F2
27. McCulloch PR, Forkert PG, Froese AB (1988) Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 137:1185–1192
28. Meredith KS, deLemos RA, Coalson JJ, King RJ, Gerstmann DR, Kumar R, Kuehl TJ, Winter DC, Taylor A, Clark RH et al (1989) Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. J Appl Physiol 66:2150–2158
29. Moriette G, Paris-Llado J, Walti H, Escande B, Magny JF, Cambonie G, Thiriez G, Cantagrel S, Lacaze-Masmonteil T, Storme L, Blanc T, Liet JM, Andre C, Salanave B, Breart G (2001) Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. Pediatrics 107:363–372
30. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K, Oguchi K, Togari H, Nishida H, 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
31. Papile LA, Burstein J, Burstein R, Koffer H (1978) Incidence and evaluation of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. J Pediatr 92:529–534
32. Pianosi PT, Fisk M (2000) High frequency ventilation trial. Nine year follow up of lung function. Early Hum Dev 57:225–234
33. Pillow JJ, Neil H, Wilkinson MH, Ramsden CA (1999) Alveolar pressure and delivered volume are dependent on compliance during HFOV. Pediatr Res 4:A1862
34. Plavka R, Kopecky P, Sebron V, Svihovec P, Zlatohlavkova B, Janus V (1999) A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome. Intensive Care Med 25:68–75
35. Rettwitz Volk W, Veldman A, Roth B, Vierzig A, Kachel W, Varnholt V, Schlosser R, von Loewenich V (1998) A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. J Pediatr 132:249–254
36. Rimensberger PC, Beghetti M, Hanquinet S, Berner M (2000) First intention high-frequency oscillation with early lung volume optimization improves pulmonary outcome in very low birth weight infants with respiratory distress syndrome. Pediatrics 105:1202–1208
37. Shankaran S, Slovis TL, Bedard MP, Poland RL (1982) Sonographic classification of intracranial hemorrhage. A prognostic indicator of mortality, morbidity, and short term neurologic outcome. J Pediatr 100:469–475
38. Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, Papile LA, Bauer CR, Stoll BJ, Tyson JE, Shankaran S, Fanaroff AA, Donovan EF, Ehrenkranz RA, Verter J (1998) Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. Am J Obstet Gynecol 179:1632–1639
39. Swischuk LE (1977) Bubbles in hyaline membrane disease. Differentiation of three types. Radiology 122:417–426
40. Thome U, Götze-Speer B, Speer CP, Pohlandt F (1998) Comparison of pulmonary inflammatory mediators in preterm infants treated with intermittent positive pressure ventilation or high frequency oscillatory ventilation. Pediatr Res 44:330–337
41. Thome U, Kossel H, Lipowsky G, Porz F, Furste HO, Genzel Boroviczeny O, Troger J, Oppermann HC, Hogel J, Pohlandt F (1999) Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr 135:39–46
42. Thome UH, Carlo WA (2000) High-frequency ventilation in neonates. Am J Perinatol 17:1–9
43. Truog WE (1999) High-frequency ventilation versus conventional ventilation: no winner—but no loser [editorial]. J Pediatr 135:9–11
44. Vazquez de Anda GF, Gommers D, Verbrugge SJ, De Jaegere A, Lachmann B (2000) Mechanical ventilation with high positive end-expiratory pressure and small driving pressure amplitude is as effective as high-frequency oscillatory ventilation to preserve the function of exogenous surfactant in lung-lavaged rats. Crit Care Med 28:2921–2925
45. Yoder BA, Siler-Khodr T, Winter VT, Coalson JJ (2000) High-frequency oscillatory ventilation. Effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. Am J Respir Crit Care Med 162:1867–1876