Meta-analysis of elective high frequency ventilation in preterm infants with respiratory distress syndrome

Filip Cools, Martin Offringa

Abstract

Aim—To summarise the evidence on the efficacy of elective high frequency ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome.

Methods—A search from 1987 onwards was made on Embase, Medline, and the Cochrane Library. A questionnaire was also circulated during an international meeting on high frequency ventilation. To be included in the data synthesis, studies had to be randomised controlled trials comparing elective high frequency ventilation with conventional ventilation in preterm infants with respiratory failure due to respiratory distress syndrome; indices of mortality, chronic pulmonary morbidity, and other clinically relevant outcomes were compared. Studies were assessed for methodological validity according to explicit criteria.

Results—Ten studies (a total number of 1345 preterm infants) were considered for data synthesis. No difference in mortality at 28 or 30 days, nor in oxygen dependency at 28 days was found between both types of ventilation. Reduced oxygen dependency at the postconceptional age of 36 weeks (RR 0.50, 95% CI 0.32–0.78) was found, but so was an increase in grades 3 and 4 intraventricular haemorrhage (IVH) (RR 1.31, 95% CI 1.04–1.66). Those studies using a high lung volume ventilatory strategy showed a significant decrease in oxygen dependency at the postconceptional age of 36 weeks (RR 0.44, 95% CI 0.27–0.73), but no increase in severe IVH (RR 0.78, 95% CI 0.45–1.37).

Conclusions—Although high frequency ventilation reduces chronic lung disease, it seems to increase the risk of severe IVH. These results are dominated by an early study where the absence of benefit on pulmonary outcomes, and the increase in adverse neurological events, could be related to the low volume ventilatory strategy used. Recent studies, using a high lung volume approach, show better pulmonary outcomes without any increase in intracranial morbidity. Still, uncertainty remains about long term pulmonary and neurodevelopmental outcome.

(Arch Dis Child Fetal Neonatal Ed 1999;80:F15–F20)

Keywords: elective high frequency ventilation; respiratory distress syndrome; intraventricular haemorrhage

Despite advances in management, such as the use of surfactant, the mortality and morbidity of respiratory distress syndrome in premature infants remain high. Chronic pulmonary morbidity after mechanical ventilation is still a major clinical problem. In particular, very low birthweight infants are at high risk of chronic lung disease: at least one in four infants between 500 and 750 g is oxygen dependent at the postconceptional age of 36 weeks.¹ It is now thought that this lung damage is largely caused by repetitive collapse and overexpansion of surfactant deficient lungs, creating shear forces, with subsequent epithelial injury and inflammatory responses.^{2,3} In an attempt to avoid such lung injury alternative ventilation modalities were examined.

High frequency ventilation (HFV) was first described by Bohn *et al* in 1980.⁴ Animal studies showed that it could obtain effective gas exchange,⁴ and, if started soon after birth, was associated with less lung injury.⁵ The first large randomised trial in human infants investigating the efficacy and safety of HFV as the primary treatment of respiratory distress syndrome (RDS), the HIFI trial in 1989,⁶ failed to show any advantage in pulmonary outcome when compared with conventional ventilation. On the contrary, the safety of HFV was a cause for concern, as it seemed to be associated with an increase in adverse neurological events—namely, intraventricular haemorrhage and possibly periventricular leucomalacia. Several smaller clinical trials have followed, of which some demonstrated a beneficial effect of HFV and others not.^{7–11}

Recently Bhuta and Henderson-Smart published a meta-analysis of four studies comparing elective high frequency oscillatory ventilation (HFOV) with conventional ventilation in preterm infants with respiratory failure.¹² They showed that, overall, there was no significant difference in oxygen dependency at 28 days between either type. They also mentioned that the HIFI trial dominated the results. Of the four studies, only two more recent trials used the HLVS. These trials showed better results for pulmonary outcomes. This review includes additional and more recent studies and adopts a different approach by initially pooling all different types of HFV—high frequency oscillation, high frequency jet ventilation, and high frequency flow interruption.

To investigate the current virtues of elective HFV compared with conventional ventilation in the treatment of RDS in preterm infants, we performed a meta-analysis of all published

Department of
Neonatology, H3-150
Emma Children's
Hospital / Academic
Medical Centre
PO Box 22660
1100 DD Amsterdam
The Netherlands
F Cools
M Offringa

Correspondence to:
Dr M Offringa.
Email: M.Offringa@
amc.uva.nl

Accepted 19 August 1998

Table 1 Characteristics of trials included in this review

Reference	HFV type	Ventilator type	HLVS*	Surfactant	No of patients	Mean birthweight (kg)	Mean gestational age (weeks)	Mean age HFV started (hours)
Froese, 1987 ¹⁶	HFOV	HSMVB, (Metrex Instruments)	No	No	15	1.1 (0.8)	28 (1)	Not reported
HIFI, 1989 ⁶	HFOV	Hummingbird, (Senko Medical Instrument Manufacturing)	No	No	673	1.1 (0.3)	28 (2)	6 (0.5)
Carlo, 1990 ¹⁷	HFJV	Self constructed¶	No	No	42	1.4 (0.3)	30 (2)	15 (4-30)†
Clark, 1992 ⁷	HFOV	Sensormedics 3100, (Sensormedics)	Yes	No	83	1.1 (0.3)	28 (3)	9 (5)
Ogawa, 1993 ⁸	HFOV	Hummingbird BMO 20 N, (Senko Medical Instruments Manufacturing)	Yes	Yes	92	1.2 (0.3)	29 (2)	2 (2)
Gerstmann, 1996 ⁹	HFOV	Sensormedics 3100 (A), (Sensormedics)	Yes	Yes	125	1.5 (0.5)	31 (2)	3 (1)
Wiswell, 1996 ²³	HFJV	Life Pulse HFJV, (Bunnell Inc)	No	Yes	73	0.9 (0.3)	27 (2)	7 (5)
Keszler, 1997 ¹⁰	HFJV	Life Pulse HFJV, (Bunnell Inc)	Yes	Yes	130	1.0 (0.2)	27 (2)	8 (4)
Rettwitz-Volk ²⁵	HFOV	Stephan SHF 3000, (F Stephan Medizintechnik)	No	Yes	96	1.1 (0.1)	28 (1)	1 (0.5)
Plavka ¹¹ (in press)	HFOV	Sensormedics 3100A (Sensormedics)	Yes	Yes	43	0.85 (0.2)	26 (2)	Not reported‡

All values are expressed as mean (SD); * HLVS: high lung volume strategy; ¶ as described by Carlo WA *et al* in *J Pediatr* 1984;104:101-7 and by Carlon GC *et al* in *Crit Care Med* 1981;9:47-50. † Value expressed as mean (range); ‡ Ventilatory stabilisation on assigned ventilator mode according to the protocol within 3 hours after birth. HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

randomised controlled trials on this issue. We also identified current areas of uncertainty, which constitute possible issues for future studies.

Methods

Two databases, Medline (from 1987 onwards) and Embase (from 1988 onwards), were searched using the terms high frequency ventilation and high frequency jet ventilation. From the search results all randomised trials comparing the use of high frequency ventilation with conventional ventilation in neonates were selected. References of previous reviews were searched manually for trials not present in the database search. The Cochrane Library was also consulted.¹³ Information concerning unpublished trials or completed trials awaiting publication was obtained directly from experts in the field during an international meeting on HFV in October 1997 in Ovatat (Belgium).

To be included in the meta-analysis the studies had to meet the following criteria: (1) the study was a randomised controlled trial; (2) the study patients were preterm infants of less than 35 weeks of gestational age or with birthweights of less than 2000 g and with respiratory failure due to respiratory distress syndrome; (3) the intervention was the elective use of high frequency ventilation—high frequency oscillation (HFOV), high frequency jet ventilation (HFJV) or high frequency flow interruption (HFFI), started within 24 hours of birth, compared with conventional ventilation; and (4) the primary aim of the study was to keep the study patients on the assigned treatment during the whole course of the disease.

Table 2 Methodological validity of included trials

Reference	1 Selection bias		2 Performance bias		3 Attrition bias		4 Detection bias
	Randomisation	Concealed allocation	Blinding intervention	Co-intervention avoided	Centres	<10% withdrawal	Blinding outcome assessment
Froese ¹⁶	Not described	Uncertain	No	Yes	1	No	No
HIFI ⁶	Computer	Uncertain	No	Yes	11	Yes	Head US*
Carlo ¹⁷	Envelopes	Uncertain	No	Uncertain	1	Yes	No
Clark ⁷	Blind card draw	Uncertain	No	Uncertain	1	Yes	Head US + CXR†
Ogawa ⁸	Envelopes	Uncertain	No	Yes	9	Yes	Head US + CXR
Gerstmann ⁹	Blind card draw	Uncertain	No	Uncertain	3	Yes	No
Wiswell ²³	Envelopes	Uncertain	No	Uncertain	1	Yes	Head US
Keszler ¹⁰	Envelopes	Uncertain	No	No	8	Yes	No
Rettwitz-Volk ²⁵	Computer	Uncertain	No	Uncertain	3	Yes	No
Plavka ¹¹	Envelopes	Uncertain	No	Uncertain	1	Yes	CXR

* Head US = head ultrasound; † CXR = chest x ray.

The trials were assessed for methodological validity according to the guidelines of the Cochrane Collaboration by examining them on four possible biases. The question of selection bias—whether there are systematic differences in comparison groups—was answered by assessing randomisation methods. Performance bias, questioning systematic differences in care provided, apart from the intervention being evaluated, was ruled out if care providers were blinded for the intervention and if co-intervention bias was avoided. The latter is attained if detailed guidelines for general patient care, apart from the intervention, were integrated in the study protocol. Attrition bias, caused by systematic differences in withdrawal from the trial, was considered to be present if more than 10% of the study patients had been lost for results and follow up. Detection bias was assessed by investigating blinding of outcome assessment. Data on the following outcomes were extracted: mortality at 28 to 30 days of age; bronchopulmonary dysplasia (BPD), defined as oxygen dependency at the age of 28 to 30 days with radiological evidence of BPD, and chronic lung disease (CLD), defined as oxygen dependency at the postconceptional age of 36 weeks; intraventricular haemorrhage (IVH), all grades, and grades 3 (IVH with distended ventricles) and 4 (with intraparenchymatous echodensity); periventricular leucomalacia (PVL); air leak syndrome (ALS), defined as gross air leak (pneumothorax, pneumomediastinum, pneumopericardium or pneumoperitoneum) and/or pulmonary interstitial emphysema (PIE); total

Table 3 Mortality at 28 to 30 days: high frequency ventilation (HFV) versus conventional ventilation (CV)

Reference	HFV event observed/ total No of patients	CV event observed/ total No of patients	Relative risk (95% CI)
Froese, 1987	2/5	3/9	1.20 (0.29, 4.95)
HIFI, 1989	60/327	60/346	1.06 (0.77, 1.46)
Carlo, 1990	4/21	5/21	0.80 (0.25, 2.57)
Clark, 1992	5/30	3/26	1.44 (0.38, 5.47)
Ogawa, 1993	0/46	1/46	0.33 (0.01, 7.98)
Gerstmann, 1996	0/64	2/61	0.19 (0.01, 3.90)
Wiswell, 1996	6/37	4/36	1.46 (0.45, 4.75)
Rettwitz-Volk, 1998	5/46	5/50	1.09 (0.34, 3.51)
Total for all studies	82/576	83/595	1.04 (0.79, 1.37)
Total for HLVS subgroup	5/140	6/133	0.77 (0.27, 2.22)
Total for surfactant subgroup	11/193	12/193	0.94 (0.45, 1.98)
Total for HFOV subgroup	72/518	74/538	1.04 (0.77, 1.39)
Total for HFJV subgroup	10/58	9/57	1.10 (0.48, 2.49)

HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

Table 4 Bronchopulmonary dysplasia: high frequency ventilation (HFV) versus conventional ventilation (CV)

Reference	HFV event observed/ total No of patients	CV event observed/ total No of patients	Relative risk (95% CI)
Froese, 1987	0/6	2/9	0.29 (0.02, 5.08)
HIFI, 1989	130/327	141/346	0.98 (0.81, 1.17)
Carlo, 1990	7/18	7/16	0.89 (0.04, 1.98)
Clark, 1992	9/30	17/26	0.46 (0.25, 0.85)
Ogawa, 1993	17/46	15/46	1.13 (0.65, 1.99)
Gerstmann, 1996	15/64	27/61	0.53 (0.31, 0.89)
Wiswell, 1996	21/37	23/36	0.89 (0.61, 1.29)
Keszler, 1997	37/55	37/52	0.95 (0.73, 1.22)
Rettwitz-Volk, 1998	18/21	14/20	1.22 (0.88, 1.71)
Total for all studies	254/604	283/612	0.90 (0.80, 1.02)
Total for HLVS subgroup	96/216	110/205	0.83 (0.69, 0.99)
Total for surfactant subgroup	108/223	116/215	0.89 (0.75, 1.06)
Total for HFOV subgroup	189/494	216/508	0.90 (0.77, 1.04)
Total for HFJV subgroup	65/110	67/104	0.92 (0.75, 1.13)

HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

Table 5 Chronic lung disease: high frequency ventilation (HFV) versus conventional ventilation (CV)

Reference	HFV event observed/ total No of patients	CV event observed/ total No of patients	Relative risk (95% CI)
Clark, 1992	3/30	10/26	0.26 (0.08, 0.84)
Wiswell, 1996	6/37	7/36	0.83 (0.31, 2.24)
Keszler, 1997	11/55	21/52	0.50 (0.27, 0.92)
Rettwitz-Volk, 1998	0/46	0/50	Not estimable
Plavka (in press)	4/21	8/20	0.48 (0.17, 1.34)
Total for all studies	24/189	46/184	0.49 (0.32, 0.75)
Total for HLVS subgroup	18/106	39/98	0.43 (0.26, 0.70)
Total for surfactant subgroup	21/159	36/158	0.56 (0.35, 0.89)
Total for HFOV subgroup	7/97	18/96	0.35 (0.16, 0.77)
Total for HFJV subgroup	17/92	28/88	0.58 (0.34, 0.98)

HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

duration of mechanical ventilation, oxygen dependency and hospital stay; long term neurodevelopmental outcome and long term pulmonary outcome.

DATA SYNTHESIS AND SUBGROUP ANALYSES

Data extraction was done by a single author with a predefined data collection form. Data were subsequently imported in Revman 3.01 software for analysis. Meta-analysis was done using both a fixed effects model¹⁴ and a random effects model.¹⁵ Relative risks (RR) with 95% confidence interval (CI) were calculated. The assumption of comparable study populations due to poolings of relative risks was assessed based on the test on homogeneity of relative

risks. Confidence intervals for relative risks that exclude unity should be considered significant. After the initial analysis of all included trials, subgroup analyses were performed. Four subgroups were determined before analysis according to the following criteria: subgroup 1 included all trials using a high lung volume strategy (HLVS); trials were considered to comply if it was clearly mentioned in the methods that HFV was started with a mean airway pressure (or continuous distending pressure) that was 1 to 2 cm H₂O higher than with conventional ventilation, or that alveolar recruitment was obtained by progressively increasing the mean airway pressure until inspired fraction of oxygen could be weaned below 0.30; subgroup 2 included all trials where surfactant replacement was given; subgroup 3 included all trials using high-frequency oscillators; and subgroup 4 included all trials using high frequency jet ventilators.

Results

Sixteen published articles of randomised controlled trials,^{6-10 16-26} one article in preparation¹¹ and two abstracts,²⁶ of which only one had been published, were identified. Two studies^{22 24} were excluded because study patients consisted mainly of term neonates with pulmonary diseases other than RDS. In two studies,¹⁷ (Ramanathan R, Ruiz I, Tantivit P, Cayabyab R, deLemos R. High frequency oscillatory ventilation compared to conventional mechanical ventilation in preterm infants with respiratory distress syndrome. Abstract, San Diego, CA: Society for Pediatric Research;1995) HFV was used for a limited time (48 hours and 96 hours, respectively), after which according to the study protocol patients were switched back to conventional ventilation. Three studies¹⁹⁻²¹ used HFV as a rescue treatment rather than as an elective mode of ventilation. One abstract was excluded because insufficient data were available on the methods of the trial at the time of data analysis.²⁷ Nine published studies and one study in press met inclusion criteria^{6-11 16 18 23 25}; the characteristics of these studies and the results of the methodological assessment are shown in tables 1 and 2.

Nine of the 10 studies mentioned mortality at the age of 28 to 30 days. Both in the overall analysis as well as in the subgroup analyses no significant difference was found (table 3). For the overall analysis the relative risk was 1.02 with a 95% CI between 0.78 and 1.35. Nine studies explored the effect on bronchopulmonary dysplasia at the age of 28 to 30 days. There was no significant difference in BPD in the overall analysis [RR 0.91, (95% CI: 0.80, 1.03)], nor in the subgroup analyses (table 4). For the HLVS subgroup the RR was 0.84, with a 95% CI between 0.69 and 1.02.

Chronic lung disease at a postconceptional age of 36 weeks was described in five, more recent studies. There is a significant reduction in CLD both in the overall analysis [RR 0.50, (95% CI: 0.32, 0.78)] and in the subgroup analyses (table 5). The reduction is most

Table 6 Intraventricular haemorrhage grade 3 and 4: high frequency ventilation (HFV) versus conventional ventilation (CV)

Reference	HFV event observed/ total No of patients	CV event observed/ total No of patients	Relative risk (95% CI)
HIFI, 1989	84/327	63/346	1.41 (1.06, 1.88)
Clark, 1992	6/30	6/26	0.87 (0.32, 2.36)
Ogawa, 1993	2/46	1/46	2.00 (0.19, 21.30)
Gerstmann, 1996	2/56	6/55	0.33 (0.07, 1.55)
Wiswell, 1996	15/37	8/36	1.82 (0.88, 3.77)
Keszler, 1997	9/61	9/59	0.97 (0.41, 2.27)
Rettwitz-Volk, 1998	5/46	2/50	2.82 (0.55, 13.33)
Plavka (in press)	0/21	1/20	0.32 (0.01, 7.38)
Total for all studies	123/624	96/638	1.31 (1.04, 1.66)
Total for HLVS subgroup	19/214	23/206	0.78 (0.45, 1.37)
Total for surfactant subgroup	33/267	27/266	1.20 (0.76, 1.90)
Total for HFOV subgroup	99/526	79/543	1.30 (1.00, 1.69)
Total for HFJV subgroup	24/98	17/95	1.37 (0.79, 2.37)

HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

Table 7 Periventricular leucomalacia: high frequency ventilation (HFV) versus conventional ventilation (CV)

Reference	HFV event observed/ total No of patients	CV event observed/ total No of patients	Relative risk (95% CI)
HIFI, 1989	38/327	25/346	1.61 (0.99, 2.60)
Ogawa, 1993	1/46	4/46	0.25 (0.03, 2.15)
Gerstmann, 1996	4/56	3/55	1.31 (0.31, 5.58)
Wiswell, 1996	10/32	2/32	5.00 (1.19, 21.04)
Keszler, 1997	4/61	9/58	0.42 (0.14, 1.30)
Rettwitz-Volk, 1998	1/46	0/50	3.26 (0.14, 77.97)
Plavka (in press)	2/21	1/20	1.90 (0.19, 19.40)
Total for all studies	60/589	44/607	1.39 (0.96, 2.02)
Total for HLVS subgroup	11/184	17/179	0.63 (0.30, 1.30)
Total for surfactant subgroup	22/262	19/261	1.13 (0.63, 2.02)
Total for HFOV subgroup	46/496	33/517	1.45 (0.95, 2.22)
Total for HFJV subgroup	14/93	11/90	1.24 (0.59, 2.61)

HFV=high frequency ventilation; HFOV=high frequency oscillatory ventilation; HFJV=high frequency jet ventilation; CV=conventional ventilation; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; CLD=chronic lung disease; HLVS=high lung volume strategy; RR=relative risk; CI=confidence interval.

evident in the subgroup of high frequency oscillators [RR 0.35, (95% CI: 0.16, 0.77)], and in the HLVS subgroup [RR 0.44, (95% CI: 0.27, 0.73)].

The incidence of IVH was mentioned in all but one trial, and the incidence of severe (grades 3 and 4) IVH was mentioned in eight trials. There was no difference in risk in the overall analysis [RR 1.09, (95% CI: 0.96, 1.23)] or in the subgroup analyses. The risk of severe IVH was significantly higher in the HFV group, however, both when using the fixed effects model [RR 1.31, (95% CI: 1.04, 1.66)], and the random effects model [RR 1.34, (95% CI: 1.05, 1.70)] (table 6). Study outcomes all differed, however. The increased risk of severe IVH was only found in the HIFI trial [RR 1.41, (95% CI: 1.06, 1.88)], which dominates this overall analysis here. The other trials did not find a higher risk. In the subgroup analyses the difference for severe IVH was not significant, although in the subgroup of high frequency oscillators, once again dominated by the HIFI trial, a trend towards an increased risk occurred [RR 1.30, (95% CI: 1.00, 1.69)].

Of the 10 studies, seven report on the incidence of periventricular leucomalacia. In the overall analysis using the fixed effects model the RR is 1.39 (95% CI: 0.96, 2.02), and with the random effects model the RR is 1.28 with a wider non-significant 95% confidence interval (95% CI: 0.51, 3.19) (table 7). Again, this outcome varies among the studies. A higher risk for cystic PVL was evident in the

study by Wiswell [RR 5.00, (95% CI: 1.19, 21.04)]. In the HIFI trial a similar trend was present, with an RR of 1.61 (95% CI: 0.99, 2.60). The other trials did not observe a difference.

All 10 studies report on the incidence of air leaks. There is no significant difference in risk for gross air leak and/or interstitial pulmonary emphysema in the overall analysis [RR 1.06, (95% CI: 0.91, 1.23)], nor in the subgroup analyses. In the HIFI study an RR of 1.20 (95% CI: 1.00, 1.43) for air leaks is observed in the HFV group, due to a higher incidence of pneumoperitoneum (3% *vs* 1% in the conventional ventilation group).

Due to the fact that values on the duration of mechanical ventilation, oxygen dependency, and hospital stay were expressed differently in the studies—mean plus standard deviation or median with range—these data could not be pooled. Only in the study by Gerstmann was a significant reduction in duration of oxygen dependency for infants weighing more than 1 kg evident (median of 13.2 days *vs* 27.6 days for the HFV and CV group, respectively). In the same study the number of infants weighing 1 kg or less still on a ventilator on day 28 of life was significantly lower in the HFV group. In the other studies no significant differences were found in duration of oxygen dependency, mechanical ventilation, or hospital stay.

Only two studies report on the long term pulmonary outcome. In the HIFI trial a total 432 of 524 surviving study patients (82%) were followed up and pulmonary function tests performed in 223 of them (43%).²⁷ There were no significant differences in incidence of episodes of wheezing, respiratory tract infections, or hospital readmissions. Impairment of pulmonary function was similar in both groups. Ogawa performed a chest x-ray of all his study infants at the age of 1 year. He found typical evidence of bronchopulmonary dysplasia in 2% of the HFV treated patients *vs* 4% in the conventionally ventilated patients, which was not significantly different.⁸

The same two studies comment on the long term neurodevelopmental outcome. In the HIFI trial 386 of the 504 survivors (77%) were neurologically tested between the corrected age of 16 and 24 months.²⁸ The proportion of children with a normal neurodevelopmental status (Bayley score of more than 83 and no major neurological defect) is significantly lower in the HFV group (54% *vs* 65% in the conventional ventilation group). This is associated with a significantly higher incidence of hydrocephalus in the HFV group (12% *vs* 6% in the conventional ventilation group). No difference is observed in risk for, or severity of, cerebral palsy. Ogawa reports an identical incidence of developmental delay at the age of 1 year of 9% in both study groups.⁸

Discussion

We used meta-analysis to address the question of efficacy and safety of the elective use of HFV in the treatment of RDS in preterm infants. All trials were rigorously assessed for their methodological quality. Several comments can be

made. First, treatment allocation may not have been truly concealed, as this was done by the care provider in the centre where the patient was treated. In open trials true concealed allocation is only possible with central allocation by telephone and by a person not taking care of the patient, so that the patient is registered as a study patient before being allocated to a treatment group. Second, in these types of intervention studies blinding of the care providers is not possible, so all the included trials are sensitive for performance bias. Moreover, only two trials provided explicit guidelines for general patient management in the methods,^{6,8} reducing cointervention bias. In one study it was even stated that no attempt was made to control non-respiratory aspects of care.¹⁰ Blinding of outcome assessment can be achieved to a certain extent if the persons interpreting chest x-ray pictures or cerebral ultrasound scans are unaware of the treatment assignment of the patient. This was evidently not the case in all the studies and thus could lead to outcome detection bias in some studies.^{9,10,15,16,24}

The results of the overall analysis are strongly influenced by the HIFI trial, which dominates the analysis due to its large study population. This trial has been criticised because the high lung volume strategy was not used.²⁹ Investigators also probably lacked experience of the ventilators at that time. Animal studies confirm the advantages of a high lung volume strategy to minimise lung injury,^{2,30} and more recent, smaller clinical trials using this strategy show better pulmonary outcomes, without any increase in intracranial morbidity.⁹⁻¹¹

It was suggested in the HIFI trial that the increased risk of severe IVH could be explained by obstructed venous return because of the continuous positive intrathoracic pressure. Yet this could not be confirmed by animal or human studies.³¹⁻³³ Wiswell's HFJV trial showed a marked increase in periventricular leucomalacia in the HFV group. Mean PaCO₂ concentrations were significantly lower in the HFV group, however, compared with the conventional ventilation group. The negative effects of hypocarbia on cerebral blood flow are described by Volpe and have been confirmed by Fujimoto and Wiswell.³³⁻³⁶ The results of the individual trials indicate that the therapeutic margin of this ventilation technique is very narrow, and that harm can be done if it is handled without sufficient experience or extensive monitoring.

By pooling all the data we increased the power of the evidence; heterogeneity between included studies, however, can impair the qualitative aspect of the analysis. Therefore, we tested for heterogeneity and performed subgroup analyses. Meta-analyses were performed by using both the Mantel-Haenszel approach¹⁴ and the DerSimonian and Laird technique.¹⁵ The former refers to the fixed-effects model and assumes that there is only one true effect of the intervention estimated by each study. The latter refers to the random-effects model and assumes that the studies are randomly taken from a population of studies and that there is a distribution of treatment effects, instead of a

single true effect. When studies are homogeneous, the results of both fixed effects and random effects model will be similar; if there is significant heterogeneity between studies, however, the DerSimonian and Laird approach (random effects model) will be more conservative, resulting in larger confidence intervals around the estimate of the pooled RR, thus being more likely to find no significant difference between treatments.

For some of the outcomes we did find a strong heterogeneity in separate study results. As Marlow mentioned in his annotation, there are important differences among trials concerning the intervention and the study population, which could explain the variations in the outcomes.³⁷ Different ventilators, as well as different ventilatory strategies were used for both types of ventilation. Four HFV frequencies going from 4 Hz¹⁸ up to 15 Hz^{6,8,16} were used, and in the study by Wiswell and Keszler a low frequency background conventional ventilation was used. Conventional ventilation frequencies as low as 25 breaths per minute^{6,7} and as high as 60 breaths per minute^{9,10} were used. Mean birthweight and gestational age of the study infants varies between 900 g at 26 weeks and 1500 g at 31 weeks.^{9,11} The children's postnatal age at which HFV was started also varies between 1.2 hours and 15.5 hours.^{18,25} Marlow rightly stated that, supported by animal data,² the very early use of HFV with a high lung volume strategy could be a very important factor in preventing lung injury and thus reducing chronic lung disease.³⁷

We conclude from the meta-analysis that HFV does not improve survival of premature infants with RDS, but it does reduce the risk of chronic lung disease at 36 weeks of postconceptional age. It may be associated, however, with an increased risk of severe intraventricular bleeding. Yet, from the subgroup analysis there is evidence that, if a high lung volume strategy is used, the reduction of chronic lung disease may be more pronounced, and this favourable effect is achieved without increasing the risk of severe intraventricular haemorrhage.

Several areas of uncertainty remain. First, the hypothesis that a high lung volume strategy is associated with better outcome still requires confirmation with controlled trials of sufficient size, investigating both short term as well as long term pulmonary and neurological outcomes. Cohorts should be followed up long enough and at comparable postconceptional ages, and should be assessed with reproducible and standardised tests. Second, the outcome in very preterm infants (less than 30 weeks gestational age) and very low birthweight infants (birthweight less than 1000 g), who are at highest risk of developing CLD and are most susceptible to neurological complications, is still to be investigated. Although most studies stratify their study patients according to birthweight, the results are usually not presented according to weight strata. Finally, as high frequency flow interrupters become widely used, randomised controlled trials investigating efficacy and safety of this technique of HFV are needed.

We suggest that new clinical trials be done evaluating the usefulness of the elective use of HFV, started as soon as possible after birth, applied with a high lung volume strategy, in very premature infants (less than 30 weeks gestational age and/or weighing less than 1 kg) and using the high-frequency flow interruptors. An optimal study design is important, such as centralised concealed treatment allocation, avoidance of cointervention bias, and blinding of outcome assessment. A consensus should be made on relevant outcomes so that results of these trials are of optimal quality and comparable with each other.

We thank R Plavka for providing his data, and A J M de Craen for critically appraising the manuscript.

- 1 Hack M, Horbar JD, Malloy M, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics* 1991;87:587-97.
- 2 Meredith KS, de Lemos RA, Coalson JJ, et al. Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. *J Appl Physiol* 1989;66:2150-8.
- 3 Taskar V, John J, Evander E, Robertson B, Jonson B. Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. *Am J Crit Care Med* 1997;155:313-20.
- 4 Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC. Ventilation by high-frequency oscillation. *J Appl Physiol* 1980;48:710-6.
- 5 Jackson JC, Truog WE, Standaert TA, et al. Reduction in lung injury after combined surfactant and high-frequency ventilation. *Am J Respir Crit Care Med* 1994;150:534-39.
- 6 HIFI study group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989;320:88-93.
- 7 Clark RH, Gerstmann DR, Null DM, deLemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics* 1992;89:5-12.
- 8 Ogawa Y, Miyasaka K, Kawano T, et al. A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. *Early Hum Devel* 1993;32:1-10.
- 9 Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicenter early high-frequency ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics* 1996;98:1044-57.
- 10 Keszler M, Modanlou HD, Brudno DS, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics* 1997;100:593-9.
- 11 Plavka R, Kopecký P, Sebroň V, Švilhovec P, Zlatohlávková B, Januš V. A prospective randomized comparison of conventional mechanical ventilation and high-frequency oscillatory ventilation in treatment of respiratory distress syndrome in extremely premature newborns. *Int Care Med* (In press).
- 12 Bhuta T, Henderson-Smart DJ. Elective high-frequency oscillatory ventilation versus conventional ventilation in preterm infants with pulmonary dysfunction: systematic review and meta-analyses. *Pediatrics* 1997;100. Available from: URL:<http://www.pediatrics.org/cgi/content/full/100/5/e6>.
- 13 The Cochrane Library (database on disk and CD ROM). The Cochrane Collaboration; Oxford Update Software; 1997 updated quarterly; available from BMJ Publishing Group, London.
- 14 Fleis JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45.
- 15 Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- 16 Froese AB, Butler PO, Fletcher WA, Byford LJ. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. *Anesth Analg* 1987;66:814-24.
- 17 Carlo WA, Chatburn RL, Martin RJ. Randomized trial of high-frequency jet ventilation versus conventional ventilation in respiratory distress syndrome. *J Pediatr* 1987;110:275-82.
- 18 Carlo WA, Siner B, Chatburn RL, Robertson S, Martin RJ. Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome. *J Pediatr* 1990;117:765-70.
- 19 Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. *J Pediatr* 1991;119:85-93.
- 20 HiFO study group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. *J Pediatr* 1993;122:609-19.
- 21 Pardou A, Vermeulen D, Muller MF, Detemmerman D. High-frequency ventilation and conventional mechanical ventilation in newborn babies with respiratory distress syndrome: a prospective, randomized trial. *Intensive Care Med* 1993;19:406-10.
- 22 Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. *J Pediatr* 1994;124:447-54.
- 23 Wiswell TE, Graziani LE, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics* 1996;98:1035-43.
- 24 Engle WA, Yoder MC, Andreoli SP, Darragh RK, Langefeld CD, Hui SL. Controlled prospective randomised comparison of high-frequency jet ventilation and conventional ventilation in neonates with respiratory failure and persistent pulmonary hypertension. *J Perinatol* 1997;17:3-9.
- 25 Rettwitz-Volk W, Veldman A, Roth B, et al. 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* 1998;132:249-54.
- 26 Thome U, Gotze-Speer B, Speer CP, Pohland F. Comparison of pulmonary inflammatory mediators in preterm infants treated with intermittent positive pressure ventilation on high frequency oscillatory ventilation. *Pediatr Res* 1998;44:330-7.
- 27 HIFI study group. High-frequency oscillatory ventilation compared with conventional ventilation in the treatment of respiratory failure in preterm infants: Assessment of pulmonary function at 9 months of corrected age. *J Pediatr* 1990;116:933-41.
- 28 HIFI study group. High-frequency oscillatory ventilation compared with conventional ventilation in the treatment of respiratory failure in preterm infants: Neurodevelopmental status at 16 to 24 months of postterm age. *J Pediatr* 1990;117:939-46.
- 29 Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics* 1991;87:565-7.
- 30 McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high-frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis* 1988;137:1185-92.
- 31 Kinsella JP, Gerstmann DR, Clark RH, et al. High-frequency oscillatory ventilation versus intermittent mandatory ventilation: early hemodynamic effects in the premature baboon with hyaline membrane disease. *Pediatr Res* 1991;29:160-6.
- 32 Schlösser RL, Rettwitz-Volk W, Allendorf A, Loewenich Vv. Hämodynamische Auswirkungen der hochfrequenten Oscillationsbeatmung bei Früh- und reifen Neugeborenen. *Klin Pädiatr* 1994;206:421-4.
- 33 Laubscher B, van Melle G, Fawer C-L, Sekarski N, Calame A. Haemodynamic changes during high-frequency oscillation for respiratory distress syndrome. *Arch Dis Child* 1996;74:F172-6.
- 34 Volpe JJ. Hypoxic ischemic encephalopathy: Biochemical and physiological aspects. In: *Neurology of the newborn*. 3d edn. Philadelphia: W B Saunders Co, 1995: 240-1.
- 35 Fujimoto S, Togari H, Yamaguchi N, Mizutani F, Suzuki S, Sobajima H. Hypocarbica and cystic periventricular leukomalacia in premature infants. *Arch Dis Child* 1994;71:F107-10.
- 36 Wiswell TE. Effects of hypocarbica on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics* 1996;98:918-24.
- 37 Marlow N. High-frequency ventilation and respiratory distress syndrome: do we have an answer? *Arch Dis Child* 1998;78:F1-F2.