Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data

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Summary

Background Population and study design heterogeneity has confounded previous meta-analyses, leading to uncertainty about effectiveness and safety of elective high-frequency oscillatory ventilation (HFOV) in preterm infants. We assessed effectiveness of elective HFOV versus conventional ventilation in this group.

Methods We did a systematic review and meta-analysis of individual patients' data from 3229 participants in ten randomised controlled trials, with the primary outcomes of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age, death or severe adverse neurological event, or any of these outcomes.

Findings For infants ventilated with HFOV, the relative risk of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age was 0·95 (95% CI 0·88–1·03), of death or severe adverse neurological event 1·00 (0·88–1·13), or any of these outcomes 0·98 (0·91–1·05). No subgroup of infants (eg, gestational age, birthweight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids) benefited more or less from HFOV. Ventilator type or ventilation strategy did not change the overall treatment effect.

Interpretation HFOV seems equally effective to conventional ventilation in preterm infants. Our results do not support selection of preterm infants for HFOV on the basis of gestational age, birthweight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids.

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Introduction

Despite advances in neonatal care, the risk of bronchopulmonary dysplasia remains high for very preterm infants[1] and is associated with long-term neurodevelopmental delay and pulmonary impairment.[2,3] High-frequency oscillatory ventilation (HFOV) seems to be a promising technique for reduction of ventilator-associated lung injury in animals[4] and, hence, could reduce risk of death or bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome. However, randomised controlled trials comparing elective HFOV with conventional ventilation have shown conflicting results.[5–10] Aggregate meta-analyses of trial data have been difficult to interpret because of heterogeneity in study design, patient characteristics, and outcome definition, and have limitations because interpretations are made on the basis of summary data extracted from published trial reports.[11] Therefore, important questions about the use of HFOV in preterm infants remain unanswered, including whether some preterm infants benefit more or less from HFOV than others and whether the effect of HFOV is modified by factors such as the type of high-frequency ventilator and the time of initiation of ventilation. Consequently, the use of HFOV as the main method of ventilation in preterm infants with respiratory distress syndrome remains controversial.[12]

A meta-analysis based on original study data from randomised controlled trials of every individual patient could potentially address these unresolved issues.[13] Information could be obtained for individual patients about the risk profile, details of how the study and co-interventions were done, and outcomes of interest. Variation in treatment effect according to the patient's risk profile and intervention-related effects could be explored.[14] The Prevention of Ventilator Induced Lung Injury Collaborative Group (PreVILIG collaboration) was therefore formed with investigators of the randomised controlled trials to compare elective HFOV with conventional ventilation in preterm infants with respiratory failure, and a protocol was developed to undertake a systematic review with meta-analysis of individual patients' data.

Methods

Search strategy and selection criteria

The protocol of this report has been published,[15] but is outlined here. We searched the most recent update of the Cochrane review of aggregate data (November, 2006),[11] Medline, Embase, the Cochrane Controlled Trials Register (CENTRAL, Cochrane Library Issue 4, 2008), and the Oxford Database of Perinatal Trials using the MeSH terms "high-frequency ventilation" and "infant, premature". We

searched for reports written in any language from 2006, until January, 2009 (figure 1). We asked experts in the field to identify any ongoing or unpublished trials, although no studies were identified with this strategy.

Studies were included if preterm infants (<35 weeks' gestational age) with respiratory insufficiency necessitating mechanical ventilation were randomly assigned to elective HFOV or conventional ventilation—deemed elective if used as the main method of ventilation early in the course of disease. Trials entering babies after conventional ventilation that was deemed to have failed rescue were excluded. Selection of eligible studies for inclusion and identification of risk of bias were done independently by two authors (FC, MO) and differences of opinion were resolved by discussion. Assessment details are described in an updated Cochrane review.[16]

Data collection

For all trials with the original individual patients' data available, we requested anonymised data about patient baseline characteristics (17 items), experimental intervention (four items), control intervention (six items), co-interventions (seven items), and outcome measures (16 items) for every randomly assigned infant (webappendix pp 1–2).[15] Data were checked for missing information, errors, and inconsistencies with published reports. All issues were referred to the investigators of the original studies and corrected as necessary.

The prespecified primary outcomes were death or bronchopulmonary dysplasia (defined as receipt of supplemental oxygen at 36 weeks' postmenstrual age, although the physiological requirement of supplemental oxygen, as tested by oxygen challenge, was not noted in any of the trials); death or severe brain injury (defined as grade 3 or 4 intraventricular haemorrhage,[17] cystic periventricular leucomalacia, or both, on ultrasound); and death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age or severe brain injury. In all trials deaths were included up to discharge home of the infant.

The prespecified secondary outcomes were death before discharge; bronchopulmonary dysplasia at 36 weeks' postmenstrual age in survivors; grade 3 or 4 intraventricular haemorrhage; cystic periventricular leucomalacia; gross pulmonary air leak (defined as presence of pneumothorax, pneumomediastinum, or pneumopericardium, or a combination thereof); any pulmonary air leak (defined as presence of gross pulmonary air leak or pulmonary interstitial emphysema, or both); postnatal and postmenstrual age at final extubation; total number of days on mechanical ventilation; postnatal and postmenstrual age at last day of treatment with continuous positive airway pressure; postnatal and postmenstrual age at last day of treatment with oxygen; retinopathy of prematurity stage 2 or more;[18] patent ductus arteriosus requiring treatment; patent ductus arteriosus requiring surgical ligation; crossover from assigned to alternative ventilation method because of treatment failure; and postnatal age at discharge from neonatal intensive care unit.

Statistical analyses

To explore treatment effects by patient characteristics, subgroup analyses were prespecified on the basis of gestation at delivery, birthweight for gestation, initial lung disease severity (oxygenation index at trial entry; calculated by mean airway pressure [cm H_2O]×fractional inspired oxygen concentration [F_iO_2]×100÷partial arterial oxygen tension [mm Hg]), antenatal treatment with corticosteroids, postnatal age at randomisation, and period of exposure to conventional ventilation before initiation of HFOV (time between intubation and study entry). Subgroup analyses added post hoc were sex of the infant, presence of chorioamnionitis, and timing of first dose of exogenous surfactant from study entry.

To explore effects by trial characteristics, prespecified subgroup analyses were planned by high-frequency ventilator type (SensorMedics 3100A, CareFusion, San Diego, CA, USA *vs* other oscillators *vs* flow interrupters) and by ventilation strategy both for HFOV (optimal lung volume strategy or not) and for conventional ventilation (lung protective ventilation strategy or not). A trial's HFOV strategy was considered to be optimum lung volume when the protocol specified the use of increasing mean airway pressures to open collapsed alveoli, by use of improvement in oxygenation as a clinical marker of lung volume recruitment. The conventional ventilation strategy was regarded as lung protective if the protocol described elements that were aimed at avoidance of overdistension or collapse of alveoli. The

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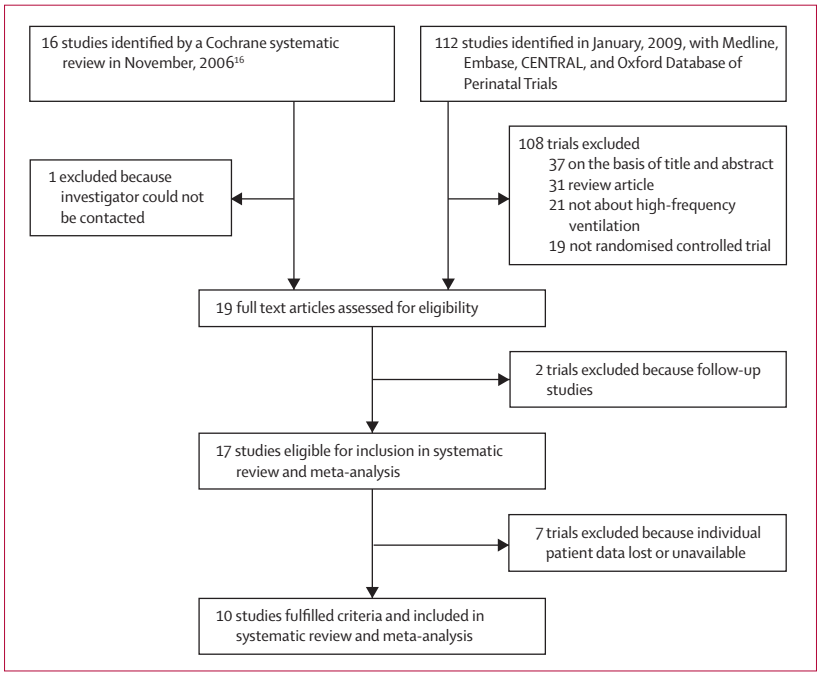

Figure 1: **Search strategy**

	HIFI[9]	Provo[6]	Thome[23]	Moriette[10]	Courtney[7]	UKOS[25]	Van Reempts[27]	Schreiber[28]	Vento[8]	Dani[29]
Trial design characteristics										
Number of centres	11	3	6	10	26	25	1	1	1	1
Number of participants	673	148	284	273	482	797	300	207	40	25
Type of HFOV	Hummingbird	SensorMedics 3100A	Infant Star	Dufour–OHF1	SensorMedics 3100A	SLE–2000HFO, SensorMedics 3100A, Dräger Babylog 8000	SensorMedics 3100A, Infant Star	SensorMedics 3100A	Dräger Babylog 8000 plus	SensorMedics 3100A
Mode of conventional ventilation	IPPV	IPPV	IPPV	SIMV	SIMV	SIMV or IPPV	IPPV	IMV	SIMV	PSV+VG
Patient characteristics										
Mean gestational age at birth (weeks; SD)	29·0 (7·0)	30·3 (2·5)	26·5 (1·6)	27·2 (1·4)	26·1 (1·6)	26·1 (1·5)	28·6 (1·8)	27·2 (2·7)	27·2 (1·3)	27·6 (1·1)
Male infants	377 (56%)	89 (60%)	164 (58%)	159 (58%)	260 (54%)	428 (54%)	..	119 (58%)	20 (50%)	12 (48%)
Infants from multiple birth	146 (22%)	..	..	81 (30%)	120 (25%)	190 (24%)	94 (36%)	38 (18%)	6 (16%)	2 (8%)
Surfactant therapy	0	125 (85%)	198 (70%)	273 (100%)	482 (100%)	769 (97%)	192 (64%)	207 (100%)	30 (75%)	25 (100%)
Median time to intubation (min; IQR)	..	11 (2–110)	12 (6–48)	3 (2–5)	3 (1–8)	2 (1–4)	53 (34–87)	0 (0–0)	0*	25 (4–79)
Median time to randomisation (min; IQR)	..	150 (81–226)	47 (24–66)	144 (92–196)	166 (118–206)	<60†	..	807 (450–1577)	20*	25 (4–79)
Antenatal corticosteroids‡	130 (21%)	34 (23%)	238 (83%)	146 (54%)	443 (92%)	727 (92%)	159 (65%)	110 (54%)	38 (95%)	20 (80%)

UKOS=UK Oscillation Study. HFOV=high-frequency oscillatory ventilation. IPPV=intermittent positive pressure ventilation. SIMV=synchronised intermittent mandatory ventilation. IMV=imtermittent mandatory ventilation. PSV+VG=pressure support ventilation with volume guarantee. ..=data not available. SD=standard deviation. IQR=interquartile range. *All infants were intubated at birth and randomly assigned at 20 min of life. †According to the study protocol infants had to be randomly assigned within the first hour of life. ‡Any antenatal treatment with corticosteroids, irrespective of the timing to delivery.

Table 1: **Characteristics of included studies**

See Online for webappendix

webappendix (p 3) details precise definitions of the ventilation strategies. The published protocol describes the prespecified subgroup analyses.[15] Definitions and subgroup analyses were designed before any data were obtained or analysed and agreed upon by consensus of the PreVILIG collaborators during group meetings.

Analyses were based on intention-to-treat and consisted of all entered infants. For every outcome, the primary analyses were restricted to trials that had at least 80% of individual patients' data available for that specific outcome. Sensitivity analyses were done to test the robustness of the results by inclusion of trials with more than 20% missing data, and by exclusion of the HIFI trial[9] (since this trial was in the presurfactant era and explicitly used a low-pressure strategy with HFOV), trials with fewer than 100 study patients, trials where assessment of brain ultrasound was not masked, and trials with a crossover rate of 20% or more in at least one treatment group. For assessment of intraventricular haemorrhage or cerebral white matter damage, a primary report from the participating centre was accepted as valid information. We regarded brain ultrasound as masked if the person interpreting the ultrasound images was unaware of the treatment assignment of the infant. Subgroup and sensitivity analyses were only done for primary outcomes.

A two-stage approach was used for the main analyses:[19] for a specific outcome the effect estimate (relative risk and 95% CI) was calculated for each trial separately and subsequently combined across trials to calculate a summary estimate. A fixed-effect model was used. The presence of heterogeneity of recorded treatment effects between trials was tested with the χ^2 test for heterogeneity and the I^2 statistic, which expresses the proportion of heterogeneity that cannot be explained by chance. Heterogeneity was deemed significant when p was less than 0·05 or I^2 was more than 50%. A random-effects model was used in all analyses to test the robustness of the results to the choice of the statistical model. In case of significant heterogeneity, results of the random-effects model are noted. We assessed risk of bias through analysis of the adequacy of random sequence generation, allocation concealment, blinding of outcome assessment (for intraventricular hemorrhage, periventricular leucomalacia, and pulmonary air leak), and completeness of follow-up data. Full details of the risk of bias assessment are published in the updated Cochrane review.[16] The analysis and plots were generated with SCHARP 4.9, a SAS-based application developed by the meta-analysis group of the Medical Research Council Clinical Trials Unit (London, UK).

Role of funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

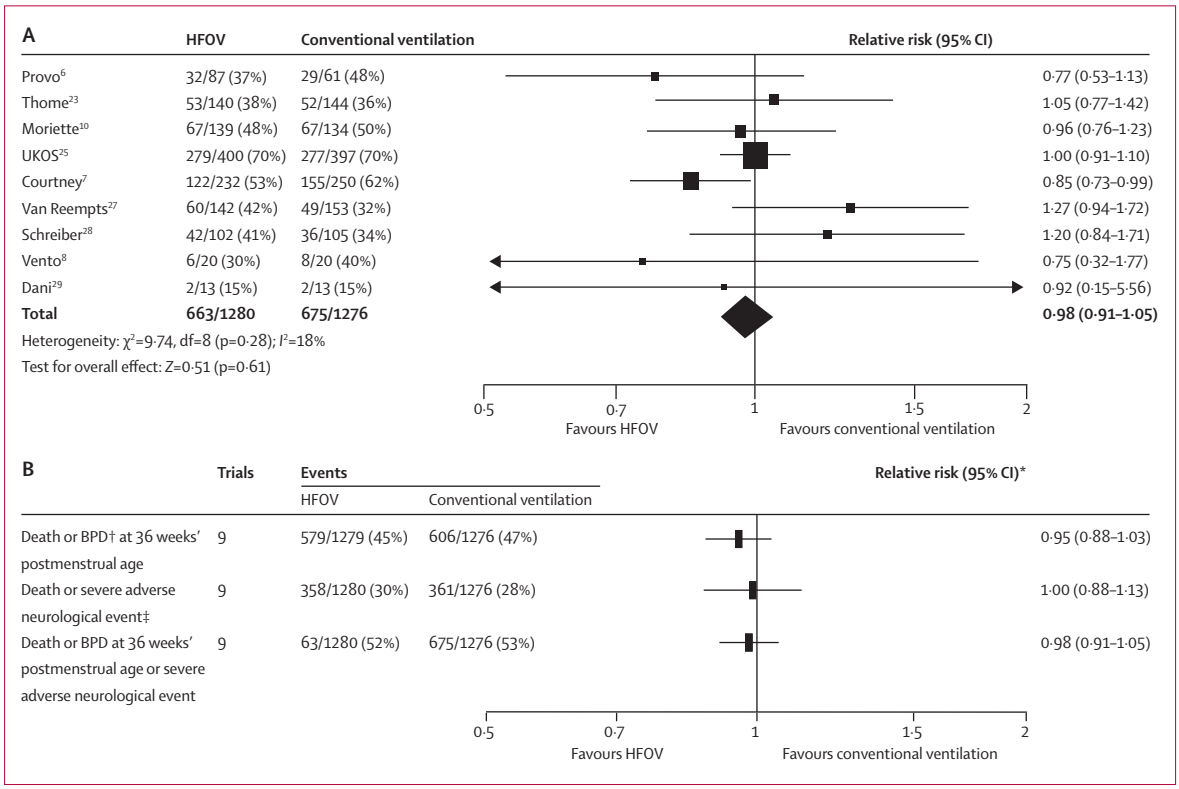

Figure 2: **Effect of HFOV compared with conventional ventilation on death or bronchopulmonary dysplasia at 36 weeks postmenstrual age or severe adverse neurological events (A), and primary outcomes (B) on the basis of individual patients' data from randomised controlled trials**

Data are n/N (%). Percentages have been rounded. Trials are ordered by year of publication in (A). HFOV=high-frequency oscillatory ventilation. *Fixed effect model. †Defined as oxygen dependency at 36 weeks' postmenstrual age. ‡Defined as intraventricular haemorrhage grade 3 or 4 according to Papile's classification[17] with or without presence of cystic periventricular leucomalacia.

Results

We identified 18 trials that were eligible for inclusion, of which 15 were from the Cochrane review,[5–10,20–28] two were from the updated search,[29,30] and one was unpublished (Texas Infant Star study, Texas Tech University School of Medicine, Odessa, TX, USA). We were unable to retrieve additional information or trace the original investigators from the unpublished trial. Thus, the 17 eligible trials reported a total of 3652 infants. In seven trials, the individual patients' data (n=430) were lost or unavailable. Individual patients' data were obtained for 3229 infants (89% of randomly assigned infants) from ten trials (table 1). The overall mean gestational age at birth was 27·3 weeks (SD 3·8) and birthweight was 989 g (315). 382 (13%) of 2922 infants had a birthweight less than the 10th percentile; 280 (12%) of 2404 infants had an Apgar score at 5 min of 5 or less; and 1748 (56%) of 3129 infants received antenatal corticosteroids. Additionally, 516 (19%) of 2762 infants were from multiple births and had a sibling within the dataset.

For the primary outcomes, use of HFOV was not associated with a significant difference in risk (figure 2) and there were no significant heterogeneities between trial results (I^2=0–18%). HFOV was not associated with an increased risk of gross pulmonary air leak, but some evidence suggests an increased risk of any pulmonary air leak, which includes pulmonary interstitial emphysema (relative risk [RR] 1·15, 95% CI 1·00–1·33). Compared with conventional ventilation, HFOV use resulted in a reduction in the need for surgical closure of patent ductus arteriosus (0·61, 0·43–0·88) and some evidence for a reduction in the risk of retinopathy of prematurity stage 2 or more (0·83, 0·71–1·00). For the risk of crossover due to treatment failure, there was a strong heterogeneity between pairs of trial results with an RR between 0·18 and 4·64 (table 2).[6,29] The postmenstrual age at final extubation was lower for HFOV than conventional ventilation with the fixed effect model, but not with a random-effects model (table 3). Some evidence suggests discontinuation of continuous positive nasal airway pressure at an earlier postmenstrual age with HFOV than with conventional ventilation. Postmenstrual age at which oxygen treatment could be stopped did not differ between the two groups (table 3).

For the three primary outcomes, effects did not differ significantly between subgroups of infants according to sex, gestational age at birth, birthweight less than the 10th percentile, presence of chorioamnionitis, oxygenation index at trial entry, antenatal treatment with

	Number of trials	Number of events (%)		Relative risk* (95% CI)
		HFOV	Conventional ventilation	
Death before discharge	9	225/1279 (18%)	237/1276 (19%)	0·96 (0·81–1·13)
BPD at 36 weeks' postmenstrual age in survivors	8	347/954 (36%)	363/935 (39%)	0·93 (0·84–1·04)
Intraventricular haemorrhage grade 3 or 4†	9	170/1231 (14%)	155/1231 (13%)	1·11 (0·90–1·35)
Cystic periventricular leucomalacia	8	61/1185 (5%)	68/1202 (6%)	0·91 (0·66–1·27)
Gross pulmonary air leak‡	10	167/1606 (10%)	157/1619 (10%)	1·08 (0·88–1·32)
Any pulmonary air leak§	10	347/1606 (22%)	301/1619 (19%)	1·15 (1·00–1·33)
Patent ductus arteriosus requiring treatment¶	9	396/1278 (31%)	418/1273 (33%)	0·94 (0·84–1·05)
Patent ductus arteriosus requiring surgery	8	44/1127 (4%)	71/1130 (6%)	0·61 (0·43–0·88)
Retinopathy of prematurity stage 2 or more‖	6	137/534 (26%)	171/554 (31%)	0·83 (0·71–1·00)
Crossover from allocated to alternative ventilation mode due to treatment failure	7	166/915 (18%)	113/891 (13%)	1·30 (0·68–2·48)**

HFOV=high-frequency oscillatory ventilation. BPD=bronchopulmonary dysplasia. *Fixed effect model is reported unless test for heterogeneity was statistically significant ($p<0·05$) or I^2 was greater than 50%. †Classification according to Papile.[17] ‡Presence of pneumothorax, pneumomediastinum, or pneumopericardium, or a combination of these disorders. §Presence of gross pulmonary air leak or pulmonary interstitial emphysema or both. ¶Treatment with anti-inflammatory drugs or surgery. ‖According to the international classification.[18] **Random-effects model, statistically significant heterogeneity for this outcome ($\chi^2=24·4$, $p<0·001$; $I^2=79·5\%$).

Table 2: **Dichotomous secondary outcomes**

	Number of trials	Number of infants		Weighted mean difference (95% CI)* HFOV versus CV
		HFOV	Conventional ventilation	
Number of days on mechanical ventilation	7	1033	1021	−1·16 (−3·95 to 1·64)†
Postnatal age (days) at final extubation	9	1240	1240	−1·18 (−3·57 to 1·21)‡
Postmenstrual age (weeks) at final extubation	9	1240	1240	−0·35 (−0·57 to −0·12)§
Postnatal age (days) at last day of nasal CPAP	4	358	379	−1·29 (−4·25 to 1·68)
Postmenstrual age (weeks) at last day of nasal CPAP	4	358	379	−0·42 (−0·85 to 0·00)
Postnatal age (days) at last day of oxygen treatment	7	843	816	−1·85 (−5·16 to 1·45)
Postmenstrual age (weeks) at last day of oxygen treatment	7	843	816	−0·41 (−0·88 to 0·07)
Postnatal age (days) at discharge	6	581	582	−0·98 (−5·01 to 3·05)

HFOV=high-frequency oscillatory ventilation. CV=conventional ventilation. CPAP=continuous positive airway pressure. *Fixed effect model is reported, unless test for heterogeneity was statistically significant ($p<0·05$) or I^2 was greater than 50%. †Random-effects model ($p=0·03$ for heterogeneity, $I^2=58\%$). ‡Random-effects model ($p=0·04$ for heterogeneity, $I^2=52\%$). §Fixed effect model. Random-effects model was −0·32 weeks (95%CI −0·66 to 0·01) ($p=0·06$ for heterogeneity, $I^2=46\%$).

Table 3: **Continuous secondary outcomes**

corticosteroids, and whether or not the course of antenatal corticosteroids was complete (table 4). The effect of HFOV was not significantly different from that of conventional ventilation when infants had received their first dose of exogenous surfactant before or after randomisation. Effect of HFOV was not modified by the postnatal age at randomisation. However, the effect of HFOV differed significantly between subgroups according to time between intubation and randomisation, showing a benefit of HFOV for reduction of deaths or bronchopulmonary dysplasia at 36 weeks' postmenstrual age or severe adverse neurological event ($p=0·01$ for interaction) if randomisation occurred between 1 h and 4 h after intubation (table 4). Also, for infants who survived, the risk of bronchopulmonary dysplasia at 36 weeks' postmenstrual age differed significantly between subgroups for infants with an intubation-to-randomisation time of 1–4 h (0·74, 0·60–0·92) by contrast with infants randomly assigned within 1 h (1·00, 0·87–1·13) or more than 4 h after intubation (1·93, 0·78–4·76; $p=0·027$ for interaction) (data not shown).

No significant differences in effect were recorded for the primary outcomes between subgroups that were based on the type of high-frequency ventilator (SensorMedics 3100A *vs* other oscillators *vs* flow interrupters) or for subgroups that were based on the intended ventilation strategy of HFOV and conventional ventilation (table 5). In figure 3, the seven trials that reported F_iO_2 and bronchopulmonary dysplasia in survivors are plotted with observed treatment effect on the risk of bronchopulmonary dysplasia in survivors (RR and 95% CI) against the median F_iO_2 in the first hours after infants were randomly assigned to the HFOV group, indicating the average efficiency of lung volume recruitment in that trial. Alveolar recruitment is associated with improved ventilation-perfusion matching and, hence, with decreased oxygen needs. Thus, a low median F_iO_2 suggests an efficient strategy

	Death or BPD at 36 weeks' postmenstrual age		Death or severe adverse neurological event		Death or BPD at 36 weeks' postmenstrual age or severe adverse neurological event	
	Relative risk (95% CI)*	Interaction p value	Relative risk (95% CI)*	Interaction p value	Relative risk (95% CI)*	Interaction p value
Sex		0·15		0·21		0·38
Male (n=1251)	0·89 (0·80–0·98)		0·92 (0·78–1·08)		0·94 (0·86–1·03)	
Female (n=1005)	1·00 (0·87–1·14)		1·06 (0·86–1·31)		0·99 (0·87–1·11)	
Gestational age		0·75		0·53		0·96
<26 weeks (n=694)	0·96 (0·87–1·05)		0·94 (0·80–1·10)		0·98 (0·90–1·07)	
26–28 weeks (n=1373)	0·94 (0·84–1·05)		1·00 (0·82–1·20)		0·97 (0·87–1·06)	
29–31 weeks (n=407)	0·89 (0·60–1·30)		0·96 (0·61–1·50)		0·93 (0·68–1·26)	
≥32 weeks (n=76)	0·72 (0·32–1·64)		3·34 (0·63–17·75)		0·94 (0·46–1·89)	
SGA		1·00		0·47		1·00
No (n=1969)	0·93 (0·85–1·02)		0·99 (0·86–1·14)		0·97 (0·89–1·05)	
Yes (n=286)	0·91 (0·77–1·06)		0·88 (0·62–1·23)		0·91 (0·78–1·07)	
Antenatal corticosteroids†		0·27		0·92		0·18
No (n=876)	0·90 (0·78–1·04)		0·99 (0·81–1·20)		0·92 (0·81–1·04)	
Yes (n=1618)	0·98 (0·89–1·04)		1·00 (0·85–1·17)		1·02 (0·94–1·11)	
Complete course of antenatal corticosteroids†‡		0·89		0·59		1·00
Yes (n=816)	1·00 (0·90–1·11)		0·95 (0·76–1·13)		1·02 (0·92–1·13)	
No (n=227)	0·96 (0·73–1·27)		0·84 (0·56–1·26)		0·97 (0·76–1·24)	
Chorioamnionitis§		0·50		0·45		0·24
No (n=1325)	0·93 (0·85–1·02)		0·98 (0·84–1·16)		0·95 (0·87–1·04)	
Yes (n=179)	1·05 (0·82–1·35)		0·79 (0·53–1·17)		1·10 (0·89–1·36)	
Oxygenation index at study entry¶		0·61		0·52		0·49
<4 (n=189)	0·72 (0·50–1·03)		0·89 (0·55–1·43)		0·75 (0·55–1·01)	
4–9 (n=425)	0·81 (0·64–1·03)		1·16 (0·86–1·58)		0·93 (0·76–1·14)	
>9 (n=399)	0·92 (0·72–1·17)		0·92 (0·69–1·23)		0·95 (0·78–1·16)	
Timing of first dose of exogenous surfactant		0·37		0·60		0·63
Before randomisation (n=1143)	0·94 (0·85–1·05)		0·93 (0·79–1·10)		0·96 (0·87–1·05)	
After randomisation (n=743)	0·89 (0·78–1·03)		1·01 (0·80–1·27)		0·93 (0·82–1·05)	
Time period from birth to randomisation (postnatal age at randomisation)		0·17		0·49		0·09
<1 h (n=1061)	0·99 (0·90–1·09)		0·98 (0·81–1·19)		1·00 (0·67–1·09)	
1–4 h (n=884)	0·84 (0·72–0·98)		0·90 (0·73–1·10)		0·87 (0·76–0·99)	
>4 h (n=287)	0·95 (0·66–1·37)		1·19 (0·84–1·69)		1·14 (0·86–1·51)	
Time from intubation to randomisation (period of conventional ventilation before HFOV)		0·06		0·59		0·014
<1 h (n=1203)	1·00 (0·91–1·10)		0·98 (0·81–1·18)		1·01 (0·93–1·11)	
1–4 h (n=780)	0·81 (0·69–0·95)		0·89 (0·72–1·09)		0·82 (0·72–0·94)‖	
>4 h (n=233)	1·03 (0·69–1·51)		1·10 (0·76–1·58)		1·18 (0·87–1·61)	

BPD=bronchopulmonary dysplasia. SGA=small for gestational age (birthweight below the 10th percentile for gestational age). HFOV=high-frequency oscillatory ventilation. F_iO_2=fractional inspired oxygen concentration. P_aO_2=partial arterial oxygen tension. *Fixed effect model is reported. †Any antenatal treatment with corticosteroids, irrespective of the timing to delivery. ‡Antenatal course of at least two doses started more than 48 h before delivery or completed more than 24 h before delivery. §Definition varied between studies, and for some studies no definition was given. ¶Oxygenation index was calculated as mean airway pressure × F_iO_2 × 100/P_aO_2. ‖Random-effects model (relative risk 0·81, 95% CI 0·66–1·00), p=0·22 for heterogeneity, I^2=31%.

Table 4: **Subgroup analyses of patient characteristics for primary outcomes**

of alveolar recruitment with HFOV. Figure 3 shows the variation between trials in efficiency of lung volume recruitment with HFOV (median F_iO_2 varied between 0·23 and 0·52).[10,27] It also shows no relation between efficiency of lung volume recruitment with HFOV in a particular trial and the recorded treatment effect in that trial.

Although more favourable results for HFOV were noted in smaller than in larger trials, the results of the meta-analyses did not change significantly when small trials were excluded. Furthermore, results did not differ when the HIFI trial[9] was included or excluded; when trials with more than 20% missing individual patients' data for a specific outcome were included; when trials with a crossover rate of 20% or more in at least one treatment group were excluded; or when trials in which masking of assessment of brain ultrasound was absent or unclear were excluded.

	Death or BPD at 36 weeks' postmenstrual age		Death or severe adverse neurological event		Death or BPD at 36 weeks' postmenstrual age or severe adverse neurological event	
	Relative risk (95% CI)*	Interaction p value	Relative risk (95% CI)*	Interaction p value	Relative risk (95% CI)*	Interaction p value
Type of high-frequency ventilator†		1·00		0·64		0·98
SensorMedics 3100A[6,7,25,27–29]	0·95 (0·83–1·09)		1·04 (0·88–1·23)		0·98 (0·88–1·11)	
Other high-frequency oscillators‡[10,25]	0·94 (0·77–1·16)		1·02 (0·83–1·24)		0·98 (0·82–1·17)	
High-frequency flow interrupter§[8,23,25,27]	0·95 (0·84–1·08)		0·91 (0·72–1·14)		0·96 (0·85–1·08)	
Ventilation strategy with HFOV and CV		0·44		0·83		0·98
No OLVS with HFOV and no LPVS with CV[9]	..		..		..	
OLVS with HFOV and no LPVS with CV[6,28]	0·86 (0·63–1·18)		1·03 (0·71–1·47)		0·99 (0·77–1·28)	
OLVS with HFOV and LPVS with CV	0·96 (0·89–1·05)		0·99 (0·87–1·13)		0·98 (0·91–1·06)	
OLVS with target F_iO_2		0·56		0·94		0·70
≤0·30[6,8,23,25,29]	0·98 (0·89–1·08)		0·97 (0·81–1·17)		1·00 (0·91–1·10)	
>0·30[7,10,27]	0·94 (0·82–1·08)		1·02 (0·85–1·22)		0·96 (0·85–1·08)	

BPD=bronchopulmonary dysplasia. HFOV=high-frequency oscillatory ventilation. CV=conventional ventilation. LPVS=lung protective ventilation strategy with conventional ventilation (see webappendix p 3 or published protocol).[15] ..=data not available. OLVS=optimum lung volume strategy with high-frequency ventilation (see webappendix p 3 or published protocol).[15] *Fixed effect model is reported. †For the two trials that used more than one type of ventilator,[25,27] the HFOV group was divided into separate groups by type of ventilator and effect estimates were calculated for every group by use of the whole CV-group as the comparator. ‡Trials using Hummingbird, SLE-2000HFO, or Dufour-OHF1. §Trials using Infant Star or Dräger Babylog 8000 plus.

Table 5: **Subgroup analyses of trial characteristics for primary outcomes**

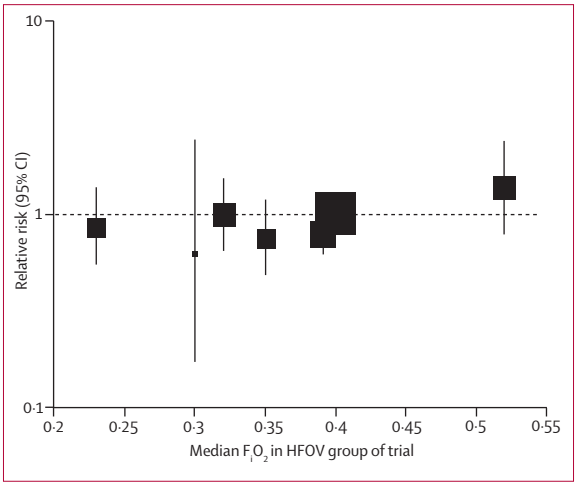

Figure 3: **Individual trial data for relative risk of bronchopulmonary dysplasia at 36 weeks', postmenstrual age in survivors and median F_iO_2 in the first hours after randomisation into HFOV groups**

F_iO_2=fractional inspired oxygen concentration. Trials are plotted as squares (with vertical lines) representing relative risk (95% CI) of bronchopulmonary dysplasia at 36 weeks' postmenstrual age in survivors, against the median F_iO_2 in the first hours after randomisation in infants in HFOV groups. Trials are plotted in order of efficiency of improvement in lung volume with HFOV—as measured by F_iO_2 after alveolar recruitment has been completed (first hours after HFOV began).

Discussion

Akin to the included studies, our meta-analysis of individual patients' data suggests that elective HFOV in preterm infants, compared with conventional ventilation, is equally effective in prevention of bronchopulmonary dysplasia without being associated with increased mortality or brain damage. Most secondary endpoints did not differ significantly between HFOV and conventional ventilation, although some evidence suggests an increase in rate of any pulmonary air leaks, and a decrease in patent ductus arteriosus requiring surgery or retinopathy of prematurity stage 2 or more with HFOV compared with conventional ventilation. Difficulty in radiological diagnosis of pulmonary interstitial emphysema makes the small increase noted in combined risk for air leak in HFOV compared with conventional ventilation a less robust outcome measure, and thus more complex to interpret. Although alveolar overdistension during conventional ventilation is harmful to the lungs,[31] little is known about the role of high inspiratory flows and distension pressures during HFOV on shear stress of the airway epithelium in the low-compliant lungs of preterm infants. Furthermore, different ventilators were used in the trials, with different frequencies and inspiration to expiration durations, which alters the mean and amplitude of alveolar pressures and tidal volumes during HFOV.[32,33] The reduction in risk of severe retinopathy of prematurity with HFOV could be linked to the optimum lung volume strategy, in which the focus lies on rapid weaning of F_iO_2. Such a strategy could have resulted in reduced exposure to high F_iO_2 in infants in the HFOV group. This hypothesis is difficult to confirm, however, since we only have data for inspired oxygen concentrations in the first 24 h after study entry. In a multivariate regression study, Termote and colleagues[34] did not see a significant correlation between HFOV and risk of retinopathy of prematurity. Our results showed that fewer infants underwent surgical ligation for a patent ductus arteriosus on HFOV than on conventional ventilation. Data for the effects of HFOV compared with conventional ventilation on ductal patency and ductal flow in preterm infants are scarce and inconsistent.[35,36] However, studies in animals have shown an increase in pulmonary vascular resistance and, hence, a decrease in left-to-right ductal shunting during lung volume recruitment manoeuvres with HFOV.[37] This mechanism could account for the less

haemodynamically significant patent ductus arteriosus seen with HFOV than with conventional ventilation.

The sizeable heterogeneity between trials in the risk of crossover caused by treatment failure is probably attributable to the differences in failure criteria (ie, blood gas values,[6,25,27] oxygenation index,[23] pulmonary air leak,[10,23,27] or haemodynamic complications[6,27]) and in the options once failure criteria were met (crossover obligatory[27] or at the discretion of the attending physician,[6,23,25] or other options besides crossover such as corticosteroids or inhaled nitric oxide[10]). For the postmenstrual age at final extubation outcome, the result was not robust to the choice of statistical method (random-effects *vs* fixed-effect model), probably because of the existing heterogeneity for this outcome. Although this suggests a possible improvement with HFOV, conclusions for this outcome should be made cautiously.

No specific subpopulations of preterm infants were identified who benefited more or less from HFOV. Also, whether the first surfactant dose was given before or after HFOV began did not modify the effect of HFOV on primary outcomes. However, infants who were randomly assigned between 1 and 4 h after intubation seemed to benefit significantly from HFOV compared with infants who were assigned very early (<1 h) or late (>4 h) after intubation. By contrast, the effect of HFOV did not differ significantly between subgroups based on postnatal age at randomisation. However, these results need to be put into context. Firstly, although exposure to conventional ventilation before HFOV and the postnatal age at the start of HFOV could both be independent effect modifiers, both variables had very similar values for most infants (overall, 83% of infants were intubated within 1 h, and 70% within 15 min of birth). The observed effect modification could therefore be the result of either or both factors. Secondly, the finding contrasts sharply with studies in animals that suggest early initiation of HFOV is critical to the protective effect, to prevent development of hyaline membrane disease and lung damage.[38] Besides that the well controlled conditions of studies in animals are often difficult to replicate in large, multicentre clinical trials, babies in clinical trials who were randomly assigned early might not have had as severe respiratory distress syndrome as the animals in the experiments.

65% of the infants assigned before 1 h came from the UK Oscillation Study (UKOS),[25] which recruited all infants needing intubation within 1 h of birth, irrespective of the severity of their lung disease. No benefit was seen from HFOV in UKOS. In the 1–4 h subgroup, 55% of infants come from the Courtney trial,[7] in which infants were recruited when, after having received the first dose of surfactant, they needed conventional ventilation with an F_iO_2 of at least 0·25 and a mean airway pressure of at least 6 cm H_2O. Significant benefit from HFOV was seen in Courtney's trial.[7] Thus, we suggest that the selective strategy of early HFOV after clear signs of progressive respiratory failure (as done by Courtney and colleagues) could be more beneficial than immediate provision of HFOV to all infants who require intubation at birth (as in UKOS[25]). This hypothesis should be further investigated.

Although our meta-analysis did not show a difference in effect according to the planned ventilation strategy, our understanding of optimum ventilation strategies evolves continuously, especially for conventional ventilation. Our analysis was based on a broad definition of gentle conventional ventilation, relevant across all periods during which these studies were undertaken. Future trials should use trial designs comparing HFOV with more contemporary definitions of gentle ventilation during conventional ventilation.

Our meta-analysis of individual patients' data provides clinically relevant information about effectiveness and safety of elective use of HFOV in preterm infants with respiratory failure, and improves on past aggregate data meta-analyses. First, the analysis was a collaborative effort involving investigators from the original trials and other experts from the start, with agreement reached through collaborative group meetings about data analysis planning and interpretation of results. Second, use of individual patients' data improved the quality of the assessment of the treatment effect because endpoints with variable definitions (eg, bronchopulmonary dysplasia) could be defined uniformly for all infants and new outcomes could be generated. Third, the analysis allowed investigation into differences in treatment effect according to patient characteristics. For clinicians caring for individual babies, knowledge that effect of HFOV is similar across various subpopulations of preterm infants is important new information. Finally, effect modification by specific ventilation strategy factors could be investigated, such as timing of initiation of HFOV or, notably, type of high-frequency ventilator used in those trials using more than one type of ventilator.

This meta-analysis has several limitations. First, the individual patients' data of 430 infants (11% of total infants randomly assigned) recruited to seven trials could not be included, because of loss of data. The large proportion of trials with missing data emphasises the importance of keeping original trial data in a safe repository for a long time. Second, central reading of brain sonograms was absent in some multicentre trials.[6,23,28] For the meta-analysis, we accepted a single primary report of the brain sonogram done at the participating centre of the study as valid, but not ideal, information. Third, although prespecified, the subgroup analyses should be interpreted cautiously. Although false-positive results could happen by chance, equally the risk of missing true effects when the number of included infants was small also exists, resulting in wide confidence intervals. Finally, the two-stage approach is a bivariate analysis investigating only one factor besides the treatment effect. The complexity of the patient's condition, clinical management, ventilator properties,

and co-interventions—such as exogenous surfactant or postnatal corticosteroids—warrants further exploration of outcomes with a multivariate modelling approach.

Overall, from meta-analysis of individual patients' data for 89% of babies entered into known randomised trials, HFOV seems as effective as conventional ventilation for important neonatal outcomes (death, oxygen dependency, and neurological injury, alone or in combination) across various subpopulations of preterm infants. Subsequent trials should investigate issues such as the optimum timing of surfactant administration in infants on HFOV and other possible roles for HFOV in the treatment of respiratory distress syndrome—for example, those infants who do not respond to initial non-invasive respiratory support.

Contributors

FC coordinated the project, participated in protocol development, data collection, data analysis and interpretation and prepared the manuscript. LMA participated in protocol development, coordinated the data management team, and participated in data analysis and interpretation. MO supervised the collaboration, and participated in protocol development and data interpretation. All the collaborators who supplied individual patients' data participated in protocol development and in data collection and interpretation. JJP and RFS participated in protocol development and data interpretation. All other authors participated actively in the writing of this manuscript by providing their comments and editing the manuscript.

Prevention of Ventilator Induced Lung Injury Collaborative Study Group (PreVILIG) collaboration

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Conflicts of interest

JJP has two SM3100A ventilators on long-term loan from Cardinal Health for research studies in animals. The PreVILIG project has been supported by an unrestricted research grant from Dräger International, manufacturer of the Babylog infant ventilator. Dräger International has not been involved in any part of the project, such as the design of the protocol, collection and analysis of the data, interpretation of the results, or preparation of the report.

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