Chapter 2

Cumulative Meta-analysis of High Frequency versus Conventional Ventilation in Premature Neonates

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Introduction

Mechanical ventilation can induce lung injury, particularly in premature and diseased lungs. There is increasing evidence that high peak inspiratory pressures and repetitive end-expiratory collapse are major determinants of lung injury [1]. This injury may extend to other organ systems, leading to multi-organ failure [2-4]. Ventilatory strategies that limit high inflation pressures and prevent end-expiratory collapse are designated as lung protective mechanical ventilation [5].

High frequency ventilation is a method of ventilation in which alveolar gas exchange is maintained by pressure swings initiating small displacements of ventilatory gases, considerably smaller than conventional tidal volumes, at frequencies generally from 5-20 Hz superimposed on a continuous positive pressure. High frequency ventilation allows higher end-expiratory pressures with lower peak inspiratory pressures and higher mean airway pressures and is therefore proposed as currently the most optimal form of lung protective ventilation [6;7].

In animal experiments, high frequency ventilation have been shown to prevent ventilator-induced lung injury [8-10]. The majority of clinical trials so far has been performed in neonates but results are equivocal. The two most recent large randomized controlled trials failed to demonstrate a significant advantage of high frequency ventilation over conventional mechanical ventilation or showed only a small benefit [11;12]. The last meta-analysis of the pooled data in neonates showed no reduction in either mortality or oxygen dependency at day 28-30 after birth but a small reduction in the risk of chronic lung disease at 36- to 37 weeks post-gestational age in patients treated with high frequency ventilation with optimized lung volume in comparison with conventional mechanical ventilation [13].

The conventional mechanical ventilation strategies for treating respiratory failure have evolved since the first published clinical trial in 1987 comparing high frequency ventilation with conventional mechanical ventilation due to the introduction of surfactant replacement therapy and the concept of lung protective ventilation [14]. Therefore, early results cannot be easily compared with later studies, a limitation that prior meta-analyses accounted for only partially or not at all [13;15-17].

We reviewed the published comparative data on high frequency ventilation and conventional mechanical ventilation in neonates and performed an updated meta-analysis including the two most recent and largest randomized clinical trials [18;19]. We stratified trials by different high frequency ventilators and by different ventilatory strategies. In addition, we performed a cumulative meta-analysis within relevant strata, which allowed us to examine the development of the available evidence over time and to assess the influence of the introduction of surfactant replacement therapy and of lung protective ventilation.

Methods

Search strategy and data collection

The Embase, Medline and Current Contents databases were searched to identify all systematic reviews and randomized controlled trials of treatment with high frequency ventilation compared with conventional mechanical ventilation. Clinical trials had to meet criteria previously adopted by Bhuta and Henderson-Smart et al. [20]. A more detailed description of the search strategy can be found in the online supplement.

Data on the following outcomes were extracted: mortality at 28 to 30 days of age; bronchopulmonary dysplasia, defined as oxygen dependency at the age of 28 to 30 days with radiologic evidence of bronchopulmonary dysplasia; chronic lung disease, defined as oxygen dependency at the postconceptional age of 36 weeks; intraventricular hemorrhage; and periventricular leukomalacia.

A high lung volume strategy with high frequency ventilation was assumed if two or more of the following items were explicitly stated in the methods: initial use of a higher mean airway pressure than on conventional mechanical ventilation; initial lowering of inspired oxygen before reducing mean airway pressure; and use of alveolar recruitment maneuvers. A lung protective strategy in the conventional mechanical ventilation group was based on specifying the Pco_2 goal, allowing permissive hypercapnia, and a high initial ventilatory rate, targeted at reducing tidal volume as previously suggested by Thome and Carlo [16].

Data analysis and statistical methods

A number of hypotheses were proposed in advance to explain differences between study outcomes. First, differences could be attributed to the type of ventilator being used. We therefore stratified studies by the following subgroups: the SensorMedics ventilator (SensorMedics, Bilthoven, The Netherlands); other high frequency oscillatory ventilators (HFOV); high frequency jet ventilators and high frequency flow interruption ventilators. Another possible explanation of different treatment effects could be the use of surfactant. Subgroups were made of studies with and studies without the concomitant use of surfactant. Finally, recent improvements in ventilation strategies could affect outcome. We therefore defined the following subgroups: no high lung volume strategy in high frequency ventilation and no lung protective strategy in conventional mechanical ventilation; high lung volume strategy in high frequency ventilation and no lung protective

strategy in conventional mechanical ventilation; high lung volume strategy in high frequency ventilation and lung protective strategy in conventional mechanical ventilation.

A cumulative meta-analysis was performed by pooling data again each time a new study was published [21]. To assess changes in relative treatment effects and identify possible sources of heterogeneity, a graph was constructed using pooled estimates and corresponding 95% confidence intervals as a function of the cumulative number of patients included in the analysis in a chronological order. The particular purpose of this graph was to show the ratio of the cumulative treatment effect to the previous cumulative treatment effect. This so-called recursive cumulative meta-analysis was created to identify graphically sources of heterogeneity emerging at specific points in time [22]. Furthermore, heterogeneity was statistically evaluated using visual examination of the extent of overlapping confidence intervals and Cochrane's Q test [23;24]. Different treatment effects were assumed in case of graphical evidence for heterogeneity and a significant test for heterogeneity ($p < 0{\cdot}10$). Differences between subgroups were statistically evaluated by a chi-square test. Meta-analyses were performed in different subgroups to eliminate heterogeneity. Cumulative meta-analyses were visualized again to assess remaining heterogeneity or changes in treatment effects. A random effects model was used to calculate pooled treatment effects. Publication bias was assessed by visual appraisal of funnel plots and performing a rank test.

Results

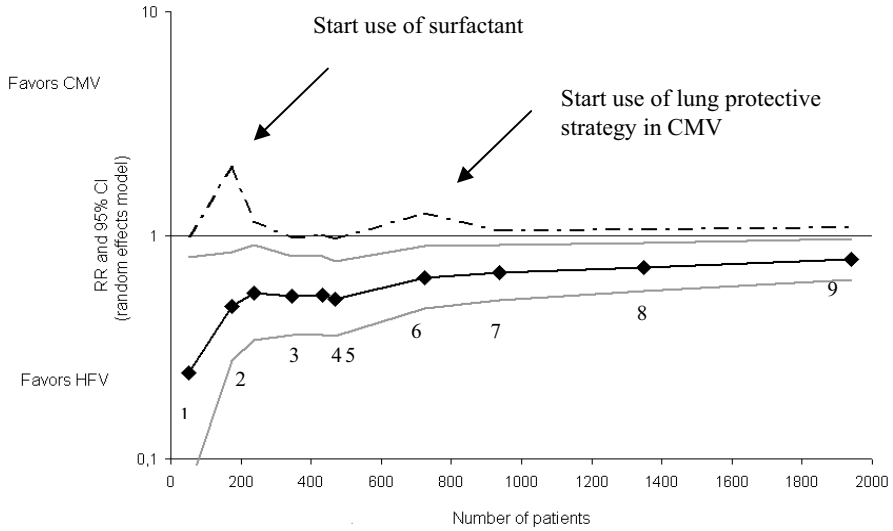
We identified five systematic reviews [13;15;16;20;25]. Using the reference lists of these systematic reviews, 14 original articles were selected. Our

literature search yielded no additional references. Thus, 14 articles were available for our analyses that represented a total of 3260 randomized patients [26-39]. The main features of these articles are summarized in the online supplement in Table E1.

There was significant heterogeneity between different studies for chronic lung disease ($p = 0.05$) and periventricular leukomalacia ($p = 0.08$) (Table E2 in the online supplement). This corresponded with significant differences between subgroups of surfactant ($p = 0.02$ for chronic lung disease and $p = 0.07$ for periventricular leukomalacia) and ventilatory strategy ($p < 0.01$ for chronic lung disease and $p = 0.02$ for periventricular leukomalacia) but not between ventilator subgroups. Significant differences between subgroups of ventilatory strategy were also detected for death or chronic lung disease ($p < 0.01$), intraventricular hemorrhage all grades ($p = 0.03$), and intraventricular hemorrhage grades 3 and 4 ($p = 0.05$) (Table E2).

Graphical presentation of the cumulative relative risk of chronic lung disease showed a distinctive shape (Figure 1). There was a convergence of the 95% confidence interval with a regression of the estimate to the line of no effect. The recursive cumulative meta-analysis was depicted by the dotted line in Figure 1. A ratio above one implied overestimation of the treatment (high frequency ventilation) effect. The first peak thus visualized corresponded with the first trial in which surfactant was used to treat respiratory distress syndrome and chronic lung disease was reported as an outcome [29]. The second peak coincided with the start of protective lung ventilation in conventional mechanical ventilation 40. Thus, the use of surfactant and lung protective strategy in conventional mechanical ventilation was graphically indicated to be two major sources of study heterogeneity.

Figure 1. Cumulative and Recursive meta-analysis of Chronic Lung Disease indicating two important sources of heterogeneity.



Cumulative and Recursive meta-analysis of Chronic Lung Disease indicating two important sources of heterogeneity. CMV: conventional mechanical ventilation. HFV: high frequency ventilation. LPVS: lung protective ventilatory strategy. X-axis: cumulative number of patients included in trials. Y-axis: relative risk (RR) and 95% CI. Diamonds: cumulative estimates of RR. Grey lines: 95% confidence intervals. Dotted line: ratio of RR estimate to prior RR estimate. A ratio > 1 indicates an overestimation of the treatment (HFV) effect. A ratio < 1 indicates an underestimation of the treatment (HFV) effect. Each diamond represents an addition of a study in the cumulative meta-analysis, the following studies were included: 1. Clark 1992; 2. Gerstmann 1996; 3. Wiswell 1996; 4. Keszler 1997; 5. Rettwitz 1998; 6. Plavka 1999; 7. Thome 1999; 8. Morriette 2001; 9. Courtney 2002; 10. Johnson 2002.

Table 1 describes the meta-analyses stratified by ventilatory strategy and ventilator subgroups with the remaining heterogeneity. In none of the ventilatory strategy subgroups was there a difference in mortality when high frequency ventilation was compared with conventional mechanical ventilation. Respiratory outcomes were better in the ventilation strategy

subgroup in which high frequency ventilation with high lung volume strategy was compared with conventional mechanical ventilation without lung protective strategy. However, high frequency ventilation without high lung volume strategy lost the ability to prevent lung damage. Furthermore, high frequency ventilation without high lung volume strategy resulted in an elevated risk of intraventricular hemorrhage, intraventricular hemorrhage grades 3 and 4 and periventricular leukomalacia. The beneficial effects on respiratory outcome also disappeared when high frequency ventilation with high lung volume strategy was compared with conventional mechanical ventilation with lung protective strategy. Remaining significant heterogeneity existed only for intraventricular hemorrhage grades 3 and 4 in the subgroup of high frequency ventilation with high lung volume strategy and conventional mechanical ventilation with lung protective strategy.

Stratification by the type of ventilator being used had less impact on treatment results and did not eliminate heterogeneity for chronic lung disease, intraventricular hemorrhage and periventricular leukomalacia (Table 1). Significantly better respiratory outcomes were reported only in the SensorMedics subgroup. In this subgroup, the relative risk of chronic lung disease was 0·57 (95% confidence interval, 0·36-0·93). However, there was significant heterogeneity , and visual examination of the cumulative meta-analysis revealed a progressive trend of the estimate of the relative risk to the line of no effect. The relative risk of death or chronic lung disease was not statistically different when high frequency ventilation with the SensorMedics was compared with conventional mechanical ventilation (relative risk = 0·67, 95% confidence interval 0·43-1·04). There was still unexplained significant heterogeneity for intraventricular hemorrhage all grades and grades 3 and 4 in the high frequency oscillatory Figure 2 is a graphical presentation of our main cumulative analysis of

Table 1. Meta-analyses in subgroups.

Ventilatory strategy subgroups

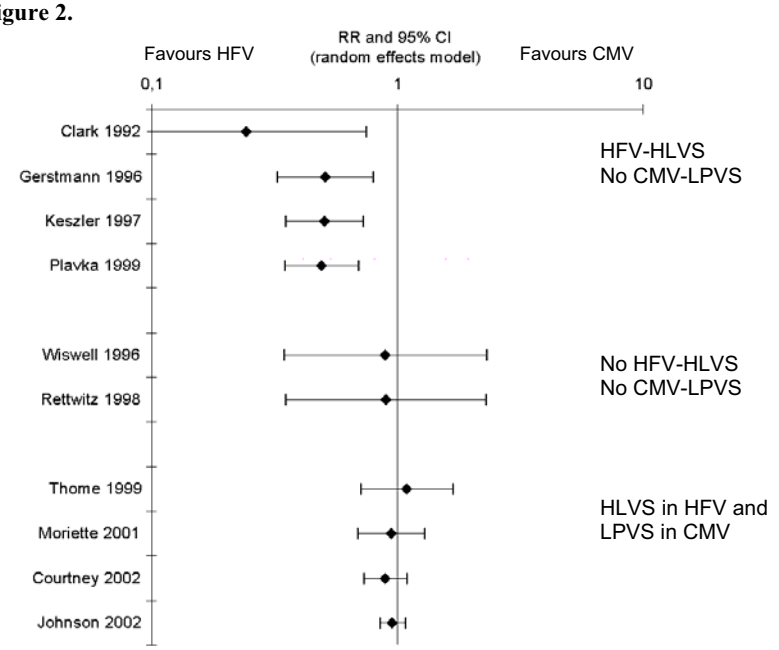
	HFV-HLVS No CMV-LPVS			No HFV-HLVS No CMV-LPVS			HFV-HLVS and CMV-LPVS		
Outcome	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub
Death	0·86 (0·52-1·44)	0·86	0·35	1·07 (0·80-1·44)	0·89	0·50	0·96 (0·80-1·15)	0·87	0·50
BPD	**0·66 (0·44-0·98)**	0·92	0·62	1·02 (0·89-1·16)	0·68	0·50	0·96 (0·81-1·13)	0·80	0·32
CLD	**0·49 (0·35-0·69)**	0·52	**0·04**	0·90 (0·35-2·29)	0·94	0·32	0·95 (0·85-1·07)	0·62	0·50
Death or CLD	**0·54 (0·38-0·77)**	0·92	0·12	~~	~~	~~	0·99 (0·91-1·07)	0·94	0·50
IVH all grades	0·95 (0·78-1·16)	0·84	0·62	**1·16 (1·01-1·34)**	0·75	1·00	0·89 (0·78-1·02)	0·36	0·60
IVH grades 3 and 4	0·85 (0·49-1·47)	0·71	0·62	**1·49 (1·14-1·94)**	0·61	0·12	1·05 (0·73-1·52)	**0·05**	0·50
PVL	0·65 (0·31-1·37)	0·42	0·50	**1·99 (1·07-3·71)**	0·32	0·60	0·86 (0·49-1·52)	0·32	0·12

Ventilator subgroups

	HFJV and HFFI			HFOV			SensorMedics		
Outcome	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub	RR (95% CI)	P het	P pub
Death	0·91 (0·58-1·43)	0·84	0·17	1·01 (0·85-1·20)	0·92	0·85	0·89 (0·61-1·30)	0·77	0·50
BPD	0·94 (0·82-1·09)	1·00	**0·05**	1·02 (0·89-1·16)	0·64	0·33	**0·51 (0·35-0·74)**	0·62	0·32
CLD	0·80 (0·48-1·35)	0·13	0·60	0·97 (0·84-1·11)	0·68	0·60	**0·57 (0·36-0·93)**	**0·06**	**0·04**
Death or CLD	~~	~~	~~	0·98 (0·89-1·07)	0·82	0·60	0·67 (0·43-1·04)	**0·02**	0·50
IVH all grades	1·04 (0·86-1·25)	0·43	0·60	0·99 (0·73-1·35)	**0·06**	0·50	0·93 (0·80-1·09)	0·83	0·33
IVH grades 3 and 4	1·25 (0·83-1·87)	0·45	0·60	1·27 (0·80-2·02)	**0·02**	0·33	0·96 (0·69-1·35)	0·54	0·50
PVL	1·99 (0·26-15·32)	**0·02**	0·60	1·30 (0·76-2·22)	0·32	0·50	0·82 (0·49-1·37)	0·61	0·12

HFV-HLVS: high frequency ventilation with high lung volume strategy. CMV-LPVS: conventional mechanical ventilation with lung protective ventilatory strategy. HFJV: high frequency jet ventilator. HFFI: high frequency flow interrupter. HFOV: high frequency oscillatory ventilator. BPD: bronchopulmonary dysplasia. CLD: chronic lung disease. IVH: intraventricular hemorrhage. PVL: periventricular leukomalacia. RR: relative risk fixed model. CI: confidence interval. ~~: insufficient data. Statistically significant results are printed in bold.

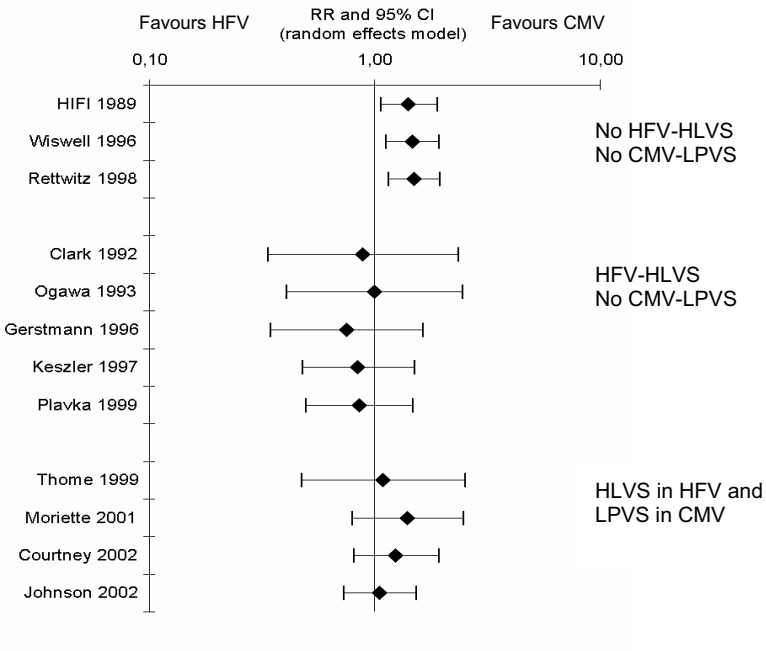
Figure 2.



Cumulative meta-analyses of Chronic Lung Disease in Ventilatory strategy subgroups. HFV: high frequency ventilation. CMV: conventional mechanical ventilation. HLVS: high lung volume strategy. LPVS: lung protective ventilatory strategy. Within each of the three subgroups of studies each later estimate is a pooled estimate of results of all previous studies. ventilation subgroup ($p = 0.06$ and p-value = 0.02, respectively) and there was significant heterogeneity for periventricular leukomalacia in the high frequency jet and high frequency flow interruption ventilator subgroup ($p = 0.02$).

chronic lung disease, which is in subgroups of ventilatory strategy. The cumulative estimate of the relative risk of chronic lung disease in high frequency ventilation with high lung volume strategy compared with conventional mechanical ventilation without a lung protective strategy did not change any further during the last three trials of the total of four studies and remained significant. The cumulative meta-analyses of chronic lung disease in the subgroup with high frequency ventilation without high lung volume strategy and the subgroup of high frequency ventilation with high lung volume strategy but also lung protective strategy in conventional

Figure 3



Cumulative meta-analyses of Intraventricular Hemorrhage in Ventilatory strategy subgroups. IVH: intraventricular hemorrhage. HFV: high frequency ventilation. CMV: conventional mechanical ventilation. HLVS: high lung volume strategy. LPVS: lung protective ventilatory strategy. Within each of the three subgroups of studies each later estimate is a pooled estimate of results of all previous studies.

of no effect. Cumulative meta-analysis of the relative risk for intraventricular hemorrhage grades 3 and 4 in the subgroup of high frequency ventilation without a high lung volume strategy showed a harmful effect compared with conventional mechanical ventilation (Figure 3). When a high lung volume strategy was being used, this effect disappeared. Thus, within comparisons of optimized high frequency ventilation and optimized conventional mechanical ventilation, including the latest large trials, there was no beneficial effect of either treatment, nor was there an indication of significant remaining heterogeneity or change in treatment effect.

Discussion

When optimized high frequency ventilation with high lung volume strategy was compared with optimized conventional mechanical ventilation with lung protective strategy there was no reduction in chronic lung disease. As in previous meta-analyses on high frequency ventilation versus conventional mechanical ventilation in neonates, we also did not find differences in mortality [13;15;16;20;25]. Cumulative meta-analysis of the data allowed us to analyze the development of the evidence and to investigate how consecutive trials contributed to the estimation of the treatment effects [19].

There is a growing understanding that clinical evidence is a dynamic process, not a static estimation of a single treatment effect at a single time point [41]. In this respect, cumulative meta-analysis should be distinguished from an updating of an existing meta-analysis. In a cumulative meta-analysis the accumulating results allow assessment of changes in patient and treatment characteristics over time. Although there was clearly significant heterogeneity, precluding pooling of estimates, a cumulative meta-analysis of chronic lung disease, including all studies, was performed exclusively to identify graphically such effects at specific points in time. As such, this analysis was not intended to calculate a single pooled treatment effect.

A first important source of heterogeneity might be small trial bias (publication bias) which results in systematic differences in effect size estimates derived from small versus large trials [42]. The other possible explanation is the improvement of conventional ventilation over time. One of the major advances in neonatal respiratory care is the introduction of surfactant [43]. Numerous clinical studies have confirmed the beneficial effect of surfactant administration on outcome of premature infants with

respiratory distress [44]. Our results indicate that introduction of surfactant therapy is reflected in a considerable change in relative treatment effects. Another advance in ventilatory care is the application of lower tidal volumes and higher positive end-expiratory pressure levels, designated as lung protective ventilation [45]. A ventilatory strategy to maintain lung volume (higher mean airway pressures) with low tidal volumes has the potential for better alveolar recruitment compared with a low volume strategy with higher tidal volumes and thus would result in better outcome in terms of chronic lung disease. Although in adult respiratory care there is increasing evidence of the beneficial effect on mortality and morbidity of lung protective ventilation [46], a large body of controversy remains [47-50]. In neonates, only few studies have addressed this topic [51;52]. We speculate that the introduction of lung protective ventilation also reflected an important change of relative treatment effects, albeit smaller than with the introduction of surfactant.

It is now generally believed that high frequency ventilation is most beneficial if the lungs are optimally recruited [53-56]. However, the evidence for this comes mainly from animal experiments [57;58]. There are no clinical studies comparing high frequency ventilation with high lung volume strategy and high frequency ventilation without high lung volume strategy. We show that the best effects of high frequency ventilation on chronic lung disease were reported in studies in which high lung volume strategy was part of the high frequency ventilation protocol but in which the conventional mechanical ventilation protocol did not meet the criteria for lung protective ventilation [29;30;33;59]. Studies not mentioning high lung volume strategy and lung protective ventilation as part of their protocol failed to show differences in effect of high frequency ventilation on chronic lung disease [34;36]. Instead these studies demonstrated an increased incidence of intraventricular hemorrhage. When lung protective conventional mechanical ventilation was compared with high frequency

ventilation with high lung volume strategy there were no differences in either chronic lung disease or intraventricular hemorrhage [35;60-62].

In previous reports it has been suggested that particularly in premature neonates with a higher baseline risk of chronic lung disease would benefit more from high frequency ventilation [35;63]. It has also been suggested that using high frequency ventilation as the primary mode of ventilation immediately after birth would increase its effectiveness [30;64]. In consecutive studies patients had lower birth weights and were more premature. In consequence this would imply a higher risk of chronic lung disease. Furthermore, institution of high frequency ventilation after birth was earlier in the more recent trials. However, our cumulative analysis of chronic lung disease showed that this did not result in a larger benefit of high frequency ventilation over conventional mechanical ventilation over time, as would have been expected.

A limitation of our analysis is the varying definitions of high lung volume strategy in the high frequency ventilation group and of lung protective strategy for conventional mechanical ventilation used in the original studies. In the definition of high lung volume strategy, a higher mean airway pressure was limited to initial use, and use of recruitment maneuvers did not necessarily mean that an open lung strategy was used the entire study period. Furthermore, the definition of lung protective ventilatory strategy did not include tidal volumes standardized to body weight or levels of positive end-expiratory pressure being applied. The actual implementation of these strategies could not be accounted for either in our analysis.

In the most recent meta-analysis published by the Cochrane Library, the use of a high lung volume strategy and treatment with surfactant was taken into account as well [13]. However, this did not eliminate existing

heterogeneity between trials. It was concluded that high frequency oscillatory ventilation caused a modest reduction in chronic lung disease. In our analyses, we did not only identify the use of surfactant as a source of heterogeneity but also the application of a lung protective strategy in the conventional mechanical ventilation group. The most significant differences between subgroups were found between trials using different ventilation strategies, not only in the high frequency ventilation group but also in the conventional mechanical ventilation group. By stratifying trials by ventilation strategies, we were able to minimize heterogeneity. We therefore explain heterogeneity between trials mainly by changes in the conventional treatment of respiratory distress in premature neonates over time. Unlike the Cochrane meta-analysis we did not find differences in chronic lung disease between optimized high frequency ventilation and optimized conventional mechanical ventilation. We suggest that future investigations should be directed towards identifying the specific pulmonary conditions in which optimized high frequency ventilation does have benefits compared with optimized conventional mechanical ventilation [65].

Cumulative meta-analysis and subsequent stratification are valuable methods to summarize and interpret the effects of changes in patient characteristics and treatments over time. These methods enabled us to show that use of surfactant and the emergence of lung protective ventilation strategies in conventional mechanical ventilation moderates the relative beneficial effect on chronic lung disease of high frequency ventilation.

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Online data supplement

Description of included studies

Included trials were assessed for methodological validity according to explicit criteria as has been described by Jadad et al E1. Disagreements about the validity score of articles were resolved by discussion. Data abstraction was not performed blinded and independently but was cross referenced to the existing meta-analyses.

All trials used valid randomization procedures. Withdrawals and dropouts were described in all trials. Follow up was sufficient (> 80%) in all included studies as well. Outcome assessment was blinded in 6 of 14 trials E2-7. However, in only 3 trials there was a clear description of how outcome blinding was achieved E4-6.

In 10 trials a high frequency oscillatory ventilator was used, in 4 of these trials this was the SensorMedics ventilator. Three studies used a high frequency jet ventilator. In one study a high frequency flow interrupter ventilator was used E10.

The first studies included patients with a mean weight ranging from 1•1 to 1•4 kg and a gestational age ranging from 28 to 30 weeks. In the last three studies birth weight ranged from 0•85 kg to 0•99 kg with a gestational age of 26 to 28 weeks. In the first trials HFV was instituted 6 to 15 hours after birth, in the last trials this was achieved 0•25 to 2•7 hours after birth. From the trial by Ogawa et al. onwards, surfactant has been used as concomitant therapy for respiratory disease E11. A high lung volume strategy was used in the first study by Froese et al E12. However, in the HIFI study and the trial by Carlo et al. this was not explicitly stated E2;8. In the last 5 reports

high lung volume strategy was specifically mentioned in the study protocol E5-7;10;13. Criteria consistent with a lung protective strategy in CMV were explicitly mentioned in the last 4 trials E5-7;10.

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Figure E1.

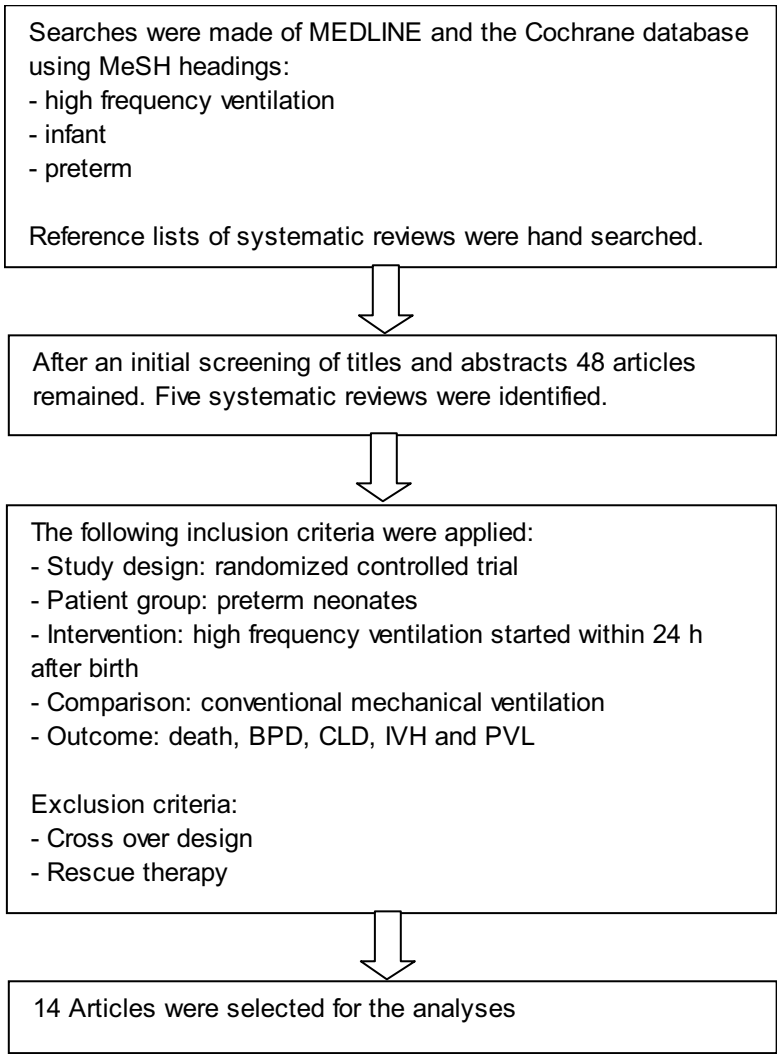
Searches were made of MEDLINE and the Cochrane database using MeSH headings:
- high frequency ventilation
- infant
- preterm
Reference lists of systematic reviews were hand searched.
After an initial screening of titles and abstracts 48 articles remained. Five systematic reviews were identified.
The following inclusion criteria were applied:
- Study design: randomized controlled trial
- Patient group: preterm neonates
- Intervention: high frequency ventilation started within 24 h after birth
- Comparison: conventional mechanical ventilation
- Outcome: death, BPD, CLD, IVH and PVL
Exclusion criteria:
- Cross over design
- Rescue therapy
14 Articles were selected for the analyses

Table E1.

Author	Year	No. of Patients Randomized	Type HFV	HF Ventilator	Mean birthweight (kg)	Mean gestational age (weeks)	Mean age HFV started (hours)	Surfactant	HFV with HLVS	CMV with LPVS	Validity
Froese	1987	15	HFOV	HSMVB, (Metrex Instruments)	1·1 (0·8)	28 (1)	Not reported	No	Yes	No	2
HIFI	1989	673	HFOV	Hummingbird, (Senko Medical Instrument Manufacturing)	1·1 (0·3)	28 (2)	6 (0·5)	No	No	No	4
Carlo	1990	42	HFJV	Research device	1·4 (0·3)	30 (2)	15 (4-30)	No	No	No	3
Clark	1992	98	HFOV	Sensormedics 3100, (Sensormedics)	1·1 (0·3)	28 (3)	9 (5)	No	Yes	No	4
Ogawa	1993	92	HFOV	Hummingbird BMO 20 N, (Senko Medical Instruments Manufacturing)	1·2 (0·3)	29 (2)	2 (2)	Yes	Yes	No	3
Gerstmann	1996	125	HFOV	Sensormedics 3100 (A), (Sensormedics)	1·5 (0·5)	31 (2)	3 (1)	Yes	Yes	No	3
Wiswell	1996	73	HFJV	Life Pulse HFJV, (Bunnell Inc)	0·9 (0·3)	27 (2)	7 (5)	Yes	No	No	5
Keszler	1997	130	HFJV	Life Pulse HFJV (Bunnell Inc)	1·0 (0·2)	27 (2)	8 (4)	Yes	Yes	No	3
Rettwitz-Volk	1998	96	HFOV	Stephan SHF 3000,(F Stephan Medizintechnik)	1·1 (0·1)	28 (1)	1 (0·5)	Yes	No	No	3
Plavka	1999	43	HFOV	Sensormedics 3100A (Sensormedics)	0·85 (0·2)	26 (2)	Not reported	Yes	Yes	No	3
Thome	1999	284	HFFI	Infant Star	0·87	27	0,5	Yes	Yes	Yes	3
Moriette	2001	292	HFOV	Dufour	0·99	28	0,25	Yes	Yes	Yes	5
Courtney	2002	500	HFOV	SensorMedics	0·85	26	2·7(0·9)	Yes	Yes	Yes	5
Johnson	2002	797	HFOV	Babylog 8000, Sensormedics, SLE 2000	0·85	26	Not reported	Yes	Yes	Yes	4

Table E2.

Outcome	*P het*	*P pub*	*P het ventilator*	*P het surfactant*	*P het strategy*
Death	0·99	0·48	0·79	0·62	0·72
BPD	0·17	**0·02**	**<0·01**	0·77	0·10
CLD	**0·05**	0·13	0·10	**0·02**	**<0·01**
Death or CLD	0·10	0·22	0·59	**0·04**	**<0·01**
IVH all grades	0·38	0·78	0·55	**0·05**	**0·03**
IVH grade 3 and 4	0·10	0·68	0·49	0·15	**0·05**
PVL	**0·08**	0·33	0·29	**0·07**	**0·02**