Prevention of ventilator induced lung injury in preterm infants with respiratory distress syndrome: PreVILIG
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CHAPTER 2A

META-ANALYSIS OF ELECTIVE HIGH FREQUENCY VENTILATION IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME

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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.

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

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. 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. 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. Animal studies showed that it could obtain effective gas exchange, and, if started soon after birth, was associated with less lung injury. 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, 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.

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. 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 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. 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 Ovifat (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.

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 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 model and a random effects model. 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 H\(_2\)O 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, one article in preparation, and two abstracts, of which only one had been published, were identified. Two studies were excluded because study patients consisted mainly of term neonates with pulmonary diseases other than RDS. In two studies, (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 studies 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.

Nine published studies and one study in press met inclusion criteria; 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 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 HIFV 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 HIFV 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 HIFV 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%). 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 HIFV treated patients vs 4% in the conventionally ventilated patients, which was not significantly different.

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. 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 HIFV group (54% vs 65% in the conventional ventilation group). This is associated with a significantly higher incidence of hydrocephalus in the HIFV 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.

DISCUSSION

We used meta-analysis to address the question of efficacy and safety of the elective use of HIFV 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, reducing cointervention bias. In one study it was even stated that no attempt was made to control non-respiratory aspects of care.

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.
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. 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, and more recent, smaller clinical trials using this strategy show better pulmonary outcomes, without any increase in intracranial morbidity.

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. 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. 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 approach and the DerSimonian and Laird technique. 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. Different ventilators, as well as different ventilatory strategies were used for both types of ventilation. Four HFV frequencies going from 4 Hz up to 15 Hz and 6 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 and as high as 60 breaths per minute were used. Mean birthweight and gestational age of the study infants varies between 900 g at 26 weeks and 1500 g at 31 weeks. The children's postnatal age at which HFV was started also varies between 1.2 hours and 15.5 hours. Marlow rightly stated that, supported by animal data, 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.

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.
### Table 1  Characteristics of trials included in this review

<table>
<thead>
<tr>
<th>Reference</th>
<th>HFV type</th>
<th>Ventilator type</th>
<th>HLVS*</th>
<th>Surfactant</th>
<th>No of patients</th>
<th>Mean birthweight (kg)</th>
<th>Mean gestational age (weeks)</th>
<th>Mean age HFV started (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froese, 1987&lt;sup&gt;16&lt;/sup&gt;</td>
<td>HF0V</td>
<td>HSMVB, (Metrox Instruments)</td>
<td>No</td>
<td>No</td>
<td>15</td>
<td>1.1 (0.8)</td>
<td>28 (1)</td>
<td>Not reported</td>
</tr>
<tr>
<td>HIFI, 1989&lt;sup&gt;9&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Hummingbird, (Senso Medical Instrument Manufacturing)</td>
<td>No</td>
<td>No</td>
<td>673</td>
<td>1.1 (0.5)</td>
<td>28 (2)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Carlo, 1990&lt;sup&gt;17&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Self constructed&lt;sup&gt;1&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>42</td>
<td>1.4 (0.3)</td>
<td>30 (2)</td>
<td>15 (4-30)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clark, 1992&lt;sup&gt;7&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Sensormedics 3100b, (Sensormedics)</td>
<td>Yes</td>
<td>No</td>
<td>83</td>
<td>1.1 (0.3)</td>
<td>28 (3)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Ogarra, 1993&lt;sup&gt;3&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Hummingbird BMO 20 N, (Senso Medical Instruments Manufacturing)</td>
<td>Yes</td>
<td>Yes</td>
<td>92</td>
<td>1.2 (0.3)</td>
<td>29 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Gerstmann, 1996&lt;sup&gt;6&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Sensormedics 3100 (A), (Sensormedics)</td>
<td>Yes</td>
<td>Yes</td>
<td>125</td>
<td>1.5 (0.5)</td>
<td>51 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Wiswell, 1996&lt;sup&gt;15&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Life Pulse HFIV, (Bunnell Inc)</td>
<td>No</td>
<td>Yes</td>
<td>73</td>
<td>0.8 (0.5)</td>
<td>27 (2)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Kessler, 1997&lt;sup&gt;10&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Life Pulse HFIV (Bunnell Inc)</td>
<td>Yes</td>
<td>Yes</td>
<td>136</td>
<td>1.0 (0.4)</td>
<td>27 (2)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Rettwitz-Volk&lt;sup&gt;5&lt;/sup&gt;</td>
<td>HF0V</td>
<td>Stephan SHF 3000b, (F Stephan Mediotechnik)</td>
<td>Yes</td>
<td>Yes</td>
<td>96</td>
<td>1.2 (0.4)</td>
<td>28 (1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Plavka&lt;sup&gt;11&lt;/sup&gt; (in press)</td>
<td>HF0V</td>
<td>Sensormedics 3100A (Sensormedics)</td>
<td>Yes</td>
<td>Yes</td>
<td>43</td>
<td>0.85 (0.2)</td>
<td>26 (2)</td>
<td>Not reported&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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; HF0V=high frequency oscillatory ventilation; HFIV=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 2  Methodological validity of included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>1 Selection bias</th>
<th>Concealed allocation</th>
<th>2 Performance bias</th>
<th>Blinding intervention</th>
<th>Co-intervention avoided</th>
<th>Centres</th>
<th>3 Attrition bias &lt;10% withdrawal</th>
<th>4 Detection bias</th>
<th>Blinding outcome assessment</th>
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<tr>
<td>Froese&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Not described</td>
<td>Uncertain</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Head US*</td>
</tr>
<tr>
<td>HIFI&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Computer</td>
<td>Uncertain</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US + CXR†</td>
</tr>
<tr>
<td>Carlo&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Envelopes</td>
<td>Uncertain</td>
<td>No</td>
<td>Uncertain</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US</td>
</tr>
<tr>
<td>Clark&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Blind card draw</td>
<td>Uncertain</td>
<td>No</td>
<td>Uncertain</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US + CXR</td>
</tr>
<tr>
<td>Ogarra&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Envelopes</td>
<td>Uncertain</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US + CXR</td>
</tr>
<tr>
<td>Gerstmann&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Blind card draw</td>
<td>Uncertain</td>
<td>No</td>
<td>Uncertain</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US</td>
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<td>Wiswell&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Envelopes</td>
<td>Uncertain</td>
<td>No</td>
<td>Uncertain</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US</td>
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<tr>
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<td>No</td>
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<td>8</td>
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<td>No</td>
<td>No</td>
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<td>No</td>
<td>Uncertain</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Head US</td>
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<tr>
<td>Plavka&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Envelopes</td>
<td>Uncertain</td>
<td>No</td>
<td>Uncertain</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>CXR</td>
</tr>
</tbody>
</table>

* Head US = head ultrasound; † CXR = chest x ray.
Table 3  Mortality at 28 to 30 days: high frequency ventilation (HFV) versus conventional ventilation (CV)

<table>
<thead>
<tr>
<th>Reference</th>
<th>HFV event observed/ total No of patients</th>
<th>CV event observed/ total No of patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froese, 1987</td>
<td>2/5</td>
<td>3/9</td>
<td>1.20 (0.29, 4.93)</td>
</tr>
<tr>
<td>HIF, 1989</td>
<td>60/327</td>
<td>60/346</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>Carlo, 1990</td>
<td>4/21</td>
<td>5/21</td>
<td>0.80 (0.25, 2.57)</td>
</tr>
<tr>
<td>Clark, 1992</td>
<td>5/30</td>
<td>3/26</td>
<td>1.44 (0.38, 5.47)</td>
</tr>
<tr>
<td>Ogawa, 1993</td>
<td>0/46</td>
<td>1/46</td>
<td>0.33 (0.01, 7.98)</td>
</tr>
<tr>
<td>Gerstmann, 1996</td>
<td>0/6</td>
<td>2/61</td>
<td>0.19 (0.01, 3.90)</td>
</tr>
<tr>
<td>Wiswell, 1996</td>
<td>6/37</td>
<td>4/36</td>
<td>1.46 (0.45, 4.75)</td>
</tr>
<tr>
<td>Rettwitz-Volk, 1998</td>
<td>5/46</td>
<td>5/50</td>
<td>1.00 (0.34, 3.51)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Reference</th>
<th>HFV event observed/ total No of patients</th>
<th>CV event observed/ total No of patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froese, 1987</td>
<td>0/6</td>
<td>2/9</td>
<td>0.29 (0.02, 5.08)</td>
</tr>
<tr>
<td>HIF, 1989</td>
<td>130/327</td>
<td>141/346</td>
<td>0.98 (0.81, 1.17)</td>
</tr>
<tr>
<td>Carlo, 1990</td>
<td>7/18</td>
<td>7/16</td>
<td>0.89 (0.04, 1.96)</td>
</tr>
<tr>
<td>Clark, 1992</td>
<td>9/30</td>
<td>17/26</td>
<td>0.46 (0.25, 0.85)</td>
</tr>
<tr>
<td>Ogawa, 1993</td>
<td>17/46</td>
<td>15/46</td>
<td>1.13 (0.65, 1.99)</td>
</tr>
<tr>
<td>Gerstmann, 1996</td>
<td>15/64</td>
<td>27/61</td>
<td>0.53 (0.31, 0.89)</td>
</tr>
<tr>
<td>Wiswell, 1996</td>
<td>21/37</td>
<td>23/36</td>
<td>0.89 (0.61, 1.29)</td>
</tr>
<tr>
<td>Keszler, 1997</td>
<td>37/55</td>
<td>37/52</td>
<td>0.95 (0.73, 1.22)</td>
</tr>
<tr>
<td>Rettwitz-Volk, 1998</td>
<td>18/21</td>
<td>14/20</td>
<td>1.22 (0.88, 1.71)</td>
</tr>
</tbody>
</table>

Total for all studies 254/604 283/612 0.90 (0.86, 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)

<table>
<thead>
<tr>
<th>Reference</th>
<th>HFV event observed/ total No of patients</th>
<th>CV event observed/ total No of patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark, 1992</td>
<td>3/30</td>
<td>10/26</td>
<td>0.26 (0.08, 0.84)</td>
</tr>
<tr>
<td>Wissel, 1996</td>
<td>6/37</td>
<td>7/36</td>
<td>0.83 (0.31, 2.24)</td>
</tr>
<tr>
<td>Kestler, 1997</td>
<td>11/55</td>
<td>21/52</td>
<td>0.50 (0.27, 0.92)</td>
</tr>
<tr>
<td>Ruttmann-Volk, 1998</td>
<td>0/46</td>
<td>0/50</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Plavka (in press)</td>
<td>4/21</td>
<td>8/20</td>
<td>0.48 (0.17, 1.34)</td>
</tr>
<tr>
<td>Total for all studies</td>
<td>24/189</td>
<td>46/184</td>
<td>0.49 (0.32, 0.73)</td>
</tr>
<tr>
<td>Total for HLVS subgroup</td>
<td>18/106</td>
<td>39/98</td>
<td>0.43 (0.26, 0.70)</td>
</tr>
<tr>
<td>Total for surfactant subgroup</td>
<td>21/159</td>
<td>36/158</td>
<td>0.56 (0.35, 0.89)</td>
</tr>
<tr>
<td>Total for HFOV subgroup</td>
<td>7/97</td>
<td>18/96</td>
<td>0.35 (0.16, 0.77)</td>
</tr>
<tr>
<td>Total for HFJV subgroup</td>
<td>17/92</td>
<td>26/89</td>
<td>0.58 (0.34, 0.98)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>HFV event observed/ total No of patients</th>
<th>CV event observed/ total No of patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPI, 1989</td>
<td>84/327</td>
<td>63/346</td>
<td>1.41 (1.06, 1.88)</td>
</tr>
<tr>
<td>Clark, 1992</td>
<td>6/30</td>
<td>6/26</td>
<td>0.87 (0.32, 2.36)</td>
</tr>
<tr>
<td>Ogawa, 1993</td>
<td>2/46</td>
<td>1/46</td>
<td>2.00 (0.19, 21.30)</td>
</tr>
<tr>
<td>Gerstmann, 1996</td>
<td>2/56</td>
<td>6/55</td>
<td>0.33 (0.07, 1.55)</td>
</tr>
<tr>
<td>Wissel, 1996</td>
<td>15/37</td>
<td>8/36</td>
<td>1.82 (0.88, 3.77)</td>
</tr>
<tr>
<td>Kestler, 1997</td>
<td>0/61</td>
<td>0/50</td>
<td>0.97 (0.41, 2.27)</td>
</tr>
<tr>
<td>Ruttmann-Volk, 1998</td>
<td>5/46</td>
<td>2/50</td>
<td>2.82 (0.55, 13.33)</td>
</tr>
<tr>
<td>Plavka (in press)</td>
<td>0/21</td>
<td>1/20</td>
<td>0.32 (0.01, 7.38)</td>
</tr>
<tr>
<td>Total for all studies</td>
<td>123/624</td>
<td>90/638</td>
<td>1.31 (1.04, 1.66)</td>
</tr>
<tr>
<td>Total for HLVS subgroup</td>
<td>19/214</td>
<td>23/200</td>
<td>0.78 (0.45, 1.37)</td>
</tr>
<tr>
<td>Total for surfactant subgroup</td>
<td>33/267</td>
<td>27/266</td>
<td>1.20 (0.76, 1.90)</td>
</tr>
<tr>
<td>Total for HFOV subgroup</td>
<td>99/526</td>
<td>79/543</td>
<td>1.30 (1.00, 1.69)</td>
</tr>
<tr>
<td>Total for HFJV subgroup</td>
<td>24/98</td>
<td>17/95</td>
<td>1.37 (0.79, 2.37)</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Reference</th>
<th>HFV event observed/total No of patients</th>
<th>CV event observed/total No of patients</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFI, 1989</td>
<td>38/327</td>
<td>25/346</td>
<td>1.61 (0.99, 2.60)</td>
</tr>
<tr>
<td>Ogniew, 1993</td>
<td>1/46</td>
<td>4/46</td>
<td>0.23 (0.03, 1.55)</td>
</tr>
<tr>
<td>Gursmann, 1996</td>
<td>4/36</td>
<td>3/25</td>
<td>1.31 (0.31, 5.28)</td>
</tr>
<tr>
<td>Wiswell, 1996</td>
<td>10/32</td>
<td>2/32</td>
<td>5.00 (1.19, 21.04)</td>
</tr>
<tr>
<td>Keszler, 1997</td>
<td>4/61</td>
<td>9/58</td>
<td>0.42 (0.14, 1.30)</td>
</tr>
<tr>
<td>Retzwit-Volk, 1998</td>
<td>1/46</td>
<td>0/50</td>
<td>3.26 (0.14, 77.97)</td>
</tr>
<tr>
<td>Plavka (in press)</td>
<td>2/21</td>
<td>1/20</td>
<td>1.90 (0.19, 19.40)</td>
</tr>
<tr>
<td>Total for all studies</td>
<td>60/589</td>
<td>44/607</td>
<td>1.39 (0.96, 2.02)</td>
</tr>
<tr>
<td>Total for HLVS subgroup</td>
<td>11/184</td>
<td>17/179</td>
<td>0.63 (0.30, 1.30)</td>
</tr>
<tr>
<td>Total for surfactant subgroup</td>
<td>22/262</td>
<td>19/261</td>
<td>1.13 (0.63, 2.02)</td>
</tr>
<tr>
<td>Total for HFOV subgroup</td>
<td>46/496</td>
<td>33/517</td>
<td>1.45 (0.95, 2.22)</td>
</tr>
<tr>
<td>Total for HFJV subgroup</td>
<td>14/93</td>
<td>11/90</td>
<td>1.24 (0.59, 2.61)</td>
</tr>
</tbody>
</table>

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.
AKNOWLEDGEMENTS

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

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ELECTIVE HIGH FREQUENCY OSCILLATORY VENTILATION VERSUS CONVENTIONAL VENTILATION FOR ACUTE PULMONARY DYSFUNCTION IN PRETERM INFANTS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS (ABSTRACT)

Published as:
Henderson-Smart DJ, Bhuta T, Cools F, Offringa M.
Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants (Cochrane Review).
ABSTRACT

Background
Respiratory failure due to lung immaturity is a major cause of mortality in preterm infants. Although intermittent positive pressure ventilation (IPPV) saves lives, lung distortion during its use is associated with lung injury and chronic lung disease (CLD). Conventional IPPV is provided at 30-80 breaths per minute while a newer form of ventilation called high frequency oscillatory ventilation (HFOV) provides 'breaths' at 10-15 seconds. This has been shown to result in less lung injury in experimental studies.

Objectives
The objective of this review is to determine whether the elective use of high frequency oscillatory ventilation (HFOV) as compared to conventional ventilation in preterm infants who are mechanically ventilated for the respiratory distress syndrome decreases the incidence of chronic lung disease (CLD) without adverse effects.

Search strategy
Searches were made of the Oxford Database of Perinatal Trials, MEDLINE, EMBASE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal handsearching by the Cochrane Collaboration, mainly in the English language. Expert informant's search in the Japanese language was made by Prof. Y. Ogawa.

Selection criteria
Randomized controlled trials comparing HFOV and CV in preterm or low birth weight infants with pulmonary dysfunction, mainly due to RDS, who are to be given IPPV. Randomization and commencement of treatment should have been as soon as possible after the start of IPPV and usually in the first 12 hours of life.

Data collection and analysis
The methodological quality of each trial was independently reviewed by the various authors. Each author extracted data separately; they were compared and differences were resolved. The standard method of the Cochrane Neonatal Review Group was used to synthesize the data using relative risk (RR) and risk difference (RD). From 1/RD the number needed to treat (NNT) for benefits, and number needed to harm (NNH) for adverse effects, were calculated.

Main results
Meta-analysis of the six eligible studies comparing HFOV with CV revealed that there is no difference in mortality. There are trends toward decreases in CLD in survivors at 28-30 days, 'death or CLD at 28-30 days' and CLD in survivors at 36-37 weeks postmenstrual age or discharge in the HFOV group. However, there are trends towards increases in severe (grades 3 & 4) intraventricular hemorrhage (IVH) and in periventricular leukomalacia (PVL) in the HFOV group. HFOV results in a small increase in any air leak syndrome (ALS), [summary RR 1.20 (1.03, 1.39)]. Only 2 trials have included neurodevelopmental follow up and more survivors in the HFOV group are abnormal [summary RR 1.26 (1.01, 1.58)]. In the subgroup of four trials where a high volume strategy (HVS) was used, HFOV results in more favourable pulmonary outcomes. There are significantly lower rates of CLD in survivors at 28-30 days [summary RR 0.53 (0.36, 0.76)] and of 'death or CLD at 28-30 days' [summary
RR 0.56 (0.40, 0.77) with a non-significant trend towards a reduction in oxygen use at 36-37 weeks postmenstrual age or discharge [summary RR 0.74 (0.55, 1.01)]. There were no differences in the rates of IVH or PVL.

Of the four trials in the subgroup using surfactant routinely, three also used the HVS. The trends in results were similar with surfactant to those for the HVS subgroup analysis. One trial suggests that HFOV may reduce the cost of in-hospital care.

In the subgroup of two trials (HIFI 1989, Rettwitz-Volk 1998) not using a HVS there is no effect of HFOV on the rate of CLD; however, there is an increase in the rate of PVL summary RR 1.64 (1.02, 2.64).

Reviewers' conclusions
The overall meta-analyses is dominated by the large HIFI study which did not use the HVS recommended on the basis of animal studies, and in which surfactant was not available. Studies which used HVS have shown some benefits in short term measures of CLD without an increase in the rates of IVH or PVL.

Caution is warranted in interpreting these results since 1) the treatment is not blinded and this could affect some outcomes; 2) radiological and ultrasound assessments of the primary outcomes were not always blinded as to treatment group; 3) the benefits and harms have not been reported in infants born at different gestational ages or of different birth weights; and 4) except for one small trial, post-neonatal survival, lung function and neurodevelopment have not been reported from HVS trials. Furthermore, results from groups experienced in the use of HFOV may not readily be generalizable.

Until these issues are resolved HFOV cannot be recommended as the routine method of giving mechanical ventilation to preterm infants with RDS. Future trials should target very preterm infants who are at most risk of CLD and infants should be randomized in gestational age strata. The economic implications along with important long term pulmonary and neurodevelopmental outcomes should be measured and reported.

The full text of this article can be obtained on request to Filip Cools (filip.cools@uzbrussel.be).
CHAPTER 2C

ELECTIVE HIGH FREQUENCY OSCILLATORY VENTILATION
VERSUS CONVENTIONAL VENTILATION
FOR ACUTE PULMONARY DYSFUNCTION
IN PRETERM INFANTS
(update Cochrane review in 2009)

Published as:
ABSTRACT

Background
Respiratory failure due to lung immaturity is a major cause of mortality in preterm infants. Although the use of intermittent positive pressure ventilation (IPPV) in neonates with respiratory failure saves lives, its use is associated with lung injury and chronic lung disease (CLD). A newer form of ventilation called high frequency oscillatory ventilation (HFOV) has been shown to result in less lung injury in experimental studies.

Objectives
The objective of this review is to determine the effect of the elective use of high frequency oscillatory ventilation (HFOV) as compared to conventional ventilation (CV) on the incidence of chronic lung disease, mortality and other complications associated with prematurity and assisted ventilation in preterm infants who are mechanically ventilated for respiratory distress syndrome (RDS).

Search strategy
Searches were made of the Oxford Database of Perinatal Trials, MEDLINE, EMBASE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching by the Cochrane Collaboration, mainly in the English language. The search was updated in January 2009.

Selection criteria
Randomised controlled trials comparing HFOV and CV in preterm or low birth weight infants with pulmonary dysfunction, mainly due to RDS, who required assisted ventilation. Randomisation and commencement of treatment needed to be as soon as possible after the start of CV and usually in the first 12 hours of life.

Data collection and analysis
The methodological quality of each trial was independently reviewed by the various authors. The standard effect measures are relative risk (RR) and risk difference (RD). From 1/RD the number needed to treat (NNT) to produce one outcome were calculated. For all measures of effect, 95% confidence intervals were used. In subgroup analyses the 99% CIs are also given for summary RRs in the text. Meta-analysis was performed using a fixed effects model. Where heterogeneity was over 50%, the random effects RR is also given.

Main results
Seventeen eligible studies of 3,652 infants were included. Meta-analysis comparing HFOV with CV revealed no evidence of effect on mortality at 28 - 30 days of age or at approximately term equivalent age. These results were consistent across studies and in subgroup analyses. The effect of HFOV on CLD in survivors at term equivalent gestational age was inconsistent across studies and the reduction was of borderline significance overall. The effect was similar in trials with a high lung volume strategy for HFOV targeting at very low FiO₂ and trials with a high lung volume strategy with somewhat higher or unspecified target FiO₂. Subgroups of trials showed a significant reduction in CLD with HFOV when no surfactant was used, when piston oscillators were used for HFOV, when lung protective strategies for CV were not used, when randomisation occurred at two to six hours of age, and when inspiratory:expiratory ratio of 1:2 was used for HFOV. In the meta-analysis of all trials, pulmonary air leaks occurred more frequently in the HFOV group.
In some studies, short-term neurological morbidity with HFOV was found, but this effect was not statistically significant overall. The subgroup of two trials not using a high volume strategy with HFOV found increased rates of Grade 3 or 4 intraventricular haemorrhage and of periventricular leukomalacia. An adverse effect of HFOV on long-term neurodevelopment was found in one large trial but not in the five other trials that reported this outcome. The rate of retinopathy of prematurity is reduced overall in the HFOV group.

Authors’ conclusions
There is no clear evidence that elective HFOV offers important advantages over CV when used as the initial ventilation strategy to treat preterm infants with acute pulmonary dysfunction. There may be a small reduction in the rate of CLD with HFOV use, but the evidence is weakened by the inconsistency of this effect across trials and the overall borderline significance. Future trials on elective HFOV should target those infants who are at most risk of CLD (extremely preterm infants), compare different strategies for generating HFOV and CV, and report important long-term neurodevelopmental outcomes.

Plain language summary
Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants
Insufficient evidence exists to support the routine use of high frequency oscillatory ventilation (HFOV) instead of conventional ventilation for preterm infants with lung disease who are given positive pressure ventilation. High frequency oscillatory ventilation is a way of providing artificial ventilation of the lungs that theoretically may produce less injury to the lungs and therefore reduce the rate of chronic lung disease. This review of the evidence from seventeen randomised controlled trials showed variable results between studies and no clear overall benefit or harm resulting from HFOV.
BACKGROUND

Pulmonary disease continues to be the major cause of morbidity and mortality in very preterm infants. Although assisted ventilation with intermittent positive pressure ventilation (IPPV) has decreased mortality, morbidity from lung injury is high. Acute injury such as pulmonary air leak was common prior to the availability of surfactant. Chronic lung disease (CLD) develops in up to one third of preterm infants with the respiratory distress syndrome (RDS) who receive IPPV. In addition to immaturity, overdistention of the lung and oxygen toxicity are thought to be important factors in the pathogenesis of CLD.

In order to avoid distortion of the lung caused by the large swings in pulmonary pressures during conventional ventilation (CV) at rates of 30 - 80, high frequency oscillatory ventilation (HFOV) at rates of 600 - 800 per minute was developed. In animal models, the use of HFOV results in more uniform lung inflation, improves oxygenation and reduces the severity of lung pathology produced by IPPV.

As discussed by Clark et al., there are strategies that reduce lung injury with both HFOV and CV. Animal studies show that lung volume maintenance with HFOV prevents lung injury. The effectiveness of HFOV might also be enhanced by the use of more powerful piston driven ventilators compared with those that generate the oscillations by flow interruption and even by certain settings with the same type of ventilator (inspiratory/expiratory ratio of 1/1 versus 1/2). Various strategies with CV appear to reduce acute lung injury. These include avoiding high tidal volumes, using positive end expiratory pressure (PEEP) and using short inspiratory times and faster rates. Allowing carbon dioxide to rise (permissive hypercapnoea) rather than increasing ventilation may also reduce lung injury in preterm infants. Many of these treatment strategies and their effects on lung injury are based on pathophysiological studies in animal models (increased cytokine release with higher tidal volumes and reduced PEEP) or trials in adults with RDS. There is evidence in preterm infants that strategies to synchronise ventilation (higher rates and patient triggered ventilation) reduce the rate of pneumothorax and the duration of ventilation, although there is no evidence that these strategies reduce CLD at 36 weeks postmenstrual age.

OBJECTIVES

The objective of this review is to determine the effect of the elective use of high frequency oscillatory ventilation (HFOV) when compared to conventional ventilation (CV) on the incidence of chronic lung disease, mortality and other complications associated with prematurity and assisted ventilation in preterm infants who are mechanically ventilated for RDS.

The following subgroup analyses pre-specified:

1. Management of HFOV: A strategy to maintain lung volume has the potential for better alveolar recruitment compared to a strategy to maintain one of low volume and thus might result in better outcomes in terms of CLD. A 'high volume strategy' (HVS) with HFOV was defined as one in which two or more of the following treatment approaches were explicitly stated in the methods: initial use of a higher mean airway pressure than on CV; initial weaning of fractional inspired oxygen before mean airway pressure; and use of alveolar recruitment manoeuvres. The fractional inspired oxygen concentration (FiO₂) is considered as being a useful clinical parameter for lung volume recruitment. Optimal alveolar recruitment is reflected by a FiO₂ which can be weaned below 0.30 or even 0.25. Therefore, trials are
classified either as "no high lung volume strategy", "high lung volume strategy with a target $\text{FiO}_2 > 0.30$ or not specified", and "high lung volume strategy with a target $\text{FiO}_2 \leq 0.30$".

2. **Surfactant replacement**: Surfactant replacement therapy would increase alveolar recruitment, attenuate RDS, and lead to less lung injury and CLD. A similar pulmonary benefit could occur in infants whose mothers received antenatal corticosteroids.

3. **Birth weight and gestational age**: Outcomes might differ in groups of infants born at different weights and gestational ages. Infants born at very low gestation and/or with very low birth weight have a higher incidence of CLD and may benefit more from HFOV. On the other hand, these infants are more susceptible to neurological complications such as intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL).

In order to explain persisting heterogeneity in the meta-analyses in previous versions of this review, the following subgroup analyses were added for the 2007 update:

4. **Type of HFOV ventilator**: True (piston) HFO ventilators might be more effective in maintaining lung volume and lead to different effects compared with those that use flow interruption. Also, differences in inspiratory:expiratory times on HFOV may affect lung injury.

5. **Management of CV**: Lung protective strategies on CV (short inspiratory times, rates of $\geq 60/\text{minute}$, PEEP of 4 - 6 cms H$2$O, limiting tidal volume, patient triggering or permissive hypercapnoea) may affect the differences between HFOV and CV.

6. **Duration of ventilation prior to randomization or age at randomization**: The treatment that infants receive prior to randomisation could alter outcomes and this could be measured by duration of ventilation prior to randomisation and/or age at randomisation.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**: Randomised or quasi-randomised controlled trials.

**Types of participants**: Preterm or low birth weight infants with pulmonary dysfunction, mainly due to RDS, who were considered to require IPPV.

**Types of interventions**: Elective HFOV vs. CV: Randomisation was accomplished early in the course of RDS soon after mechanical ventilation was begun. Such trials were classified as ‘elective’. Trials were classified as ‘rescue’, and therefore excluded from this review, when patients were randomised after failure to adequately ventilate on CV or when complications of CV developed or were likely to develop. The use of HFOV as rescue therapy and the use of elective high frequency jet ventilation are the subjects of other reviews. *(Henderson-Smart 2005; Bhuta 2003)*

Trials were not eligible if cross-over of interventions were mandatory.

**Types of outcome measures**: Outcomes from trials were not eligible if there was a 20% or greater rate of missing or unreported data.

**Primary outcomes**:
1. Mortality at 28 - 30 days and at term equivalent age
2. Chronic lung disease
   - Oxygen dependency at 28 - 30 days (with and without chest x-ray changes)
   - Oxygen dependency or use of assisted ventilation at 36 - 37 weeks postmenstrual age (PMA) or discharge
3. Death or chronic lung disease

Secondary outcomes:

4. Failure of allocated treatment to maintain gas exchange, leading to cross over to alternate treatment
5. Pulmonary air leak syndromes - all [including pulmonary interstitial emphysema - (PIE) and gross extrapulmonary air leak (such as pneumothorax)]
6. Intraventricular haemorrhage: all grades + Grades 3 (ventricles distended with blood) or 4 (parenchymal involvement)
7. Intraventricular haemorrhage: all grades + Grades 3 (ventricles distended with blood) or 4 (parenchymal involvement)
8. Retinopathy of prematurity (ROP) - grade 2 or more
9. Use of hospital resources (length of hospital stay, duration of IPPV)
10. Long-term growth and neurodevelopment

Search methods for identification of studies

Searches were made of the Oxford Database of Perinatal Trials, Cochrane Controlled Trials Register (CENTRAL, The Cochrane Library Issue 4, 2008, MEDLINE and EMBASE (using MeSH headings 'high-frequency-ventilation' and 'infant, preterm' from 1983 to January 2009), previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching by the Cochrane Collaboration, mainly in the English language. Expert informant's search in the Japanese language was made by Prof. Y. Ogawa in 1996. Abstracts of the annual meetings of Society for Pediatric Research (1996 - 2009 inclusive) were also searched.

Data collection and analysis

The standard methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group (CNRG) were used to evaluate the methodological quality of each trial. Trials were reviewed independently by each author for eligibility. Data were extracted separately by each author, then compared and any differences resolved.

Additional information was obtained from several authors (Ogawa 1993; Gerlitzmann 1996; Rattato-Volk 1998; Thome 1998; Plavka 1999; Moriette 2001; and Johnson 2002) regarding trial methodology. Schreiber (Schreiber 2003) re-analysed their trial data on use of nitric oxide to evaluate outcomes related to HFOV/CV to which the infants were also randomised. Clark (Clark 1999) and Plavka (Plavka 1999) provided information on infants excluded post-randomisation, which allowed for an intention to treat analysis. Some authors (Plavka 1999; Moriette 2001 and Van Reempts 2003) provided additional outcome information from their trials (see Table of Included Studies for details).

Results for outcomes requiring survival to a given age are reported with survivors as the denominator (IPPV, CLD ). Survival was used as the denominator for ROP, where the number examined was not given. (HIFI 1989; Schreiber 2003; Van Reempts 2003).

The standard method of the CNRG was used to analyse the data. Treatment effects were expressed using relative risk (RR) and risk difference (RD). From 1/RD the number needed to treat (NNT) to produce one outcome was calculated. For each measure the 95% confidence intervals (CI) are routinely given. In subgroup analyses the 99% CIs are also given for summary RRs in the text. Meta-analysis was performed using a fixed effects model. Where heterogeneity was over 50%, the random effects RR is also given.
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Overall, 22 randomised controlled trials of HFOV vs. CV were found, of which 17 met eligibility criteria and full trial data were available. Details of each of these included studies (HIFI 1989; Clark 1992; Ogawa 1993; Gerstmann 1996; Rettwitz-Volk 1998; Thome 1998; Plavka 1999; Moriette 2001; Durand 2001; Courtney 2002; Johnson 2002; Van Reempts 2003; Craft 2003; Schreiber 2003; Vento 2005; Dani 2006; Lista 2008) are given in the Table of Included Studies.

The study by Froese et al (Froese 1987) has not been included because after randomisation of infants (unknown gestation range) with presumed RDS, 5 of 11 in the HFOV group and an unknown number from the CV group were excluded from the comparisons between treatments. Only data on infants < 29 weeks with RDS were reported. The study by Lombet (Lombet 1996) has been excluded because there was 22% loss after randomisation. The study by Cambonie et al (Cambonie 2003) was not included as the trial only examined haemodynamic status during HFOV compared to CV and clinical outcomes were not reported.

Two other studies have been excluded from the review. The HiFO study (HiFO 1993) was excluded since HFOV was used as rescue therapy. This study is included in a separate review of HFOV (Henderson-Smart 2005). The study by Ramanathan et al (Ramanathan 1995), which has only been published in abstract form, was excluded because there was a mandatory crossover from HFOV to CV at 96 hours of age. Some information from these latter two trials concerning rates of IVH is considered in the discussion.

Participants

All but six (Clark 1992; Plavka 1999; Van Reempts 2003; Vento 2005; Dani 2006; Lista 2008) of the included studies were multicentre. The total number of infants randomised in each study varied from 25 (Dani 2006) to 797 (Johnson 2002). All studies included preterm infants, although the upper limit for birth weight or gestation differed. This upper limit for birth weight was 1001 g in one (Clark 1992), 1200 g in two (Courtney 2002; Durand 2001), 1500 g in three (Rettwitz-Volk 1998; Plavka 1999; Vento 2003), 1750 g in one (Clark 1992), 2000 g in three (Gerstmann 1996; Ogawa 1993; Schreiber 2003). Upper gestational age limits were 36 weeks in one (Gerstmann 1996), 35 weeks in one (Clark 1992), 34 weeks in two (Ogawa 1993; Schreiber 2003), 32 weeks in two (Rettwitz-Volk 1998; Thome 1998), 31 weeks in one (Van Reempts 2003), 30 weeks in three (Thome 1998; Moriette 2001; Dani 2006) and 29 weeks in two (Johnson 2002; Vento 2005). The average age at randomisation varied from less than one hour (Thome 1998; Johnson 2002; Vento 2005; Dani 2009) to 12 hours (Schreiber 2003). Each trial stratified infants at randomisation by weight or gestational age, although few data are reported by these subgroups.

Prenatal corticosteroid use was not reported in two trials (HIFI 1989; Ogawa 1993); they were used in a minority of women in two trials (Clark 1992; Gerstmann 1996) and used in 50 - 100% of women in the remaining 13 trials.

Interventions

Different ventilators were used to deliver HFOV. Seven trials used the Sensormedics 3100 (Clark 1992; Gerstmann 1996; Plavka 1999; Durand 2001; Courtney 2002; Schreiber 2003; Dani 2006), two used the Hummingbird (HIFI 1989; Ogawa 1993), one used a Stephan piston oscillator (Rettwitz-Volk 1998), one used an Infant Star ventilator (Thome 1998), one used a French piston oscillator (Moriette 2001), and two trials used Dräger Babylog ventilator (Vento 2005; Lista 2008). Two trials used more than one type of ventilator: Van reempts used either Sensormedics 3100 (83%) or Infant Star (17%) (Van Reempts 2003).
and in the UKOS trial (Johnson 2002), a variety of ventilators (Sensormedics, SLE, Dräger) were used. HFOV was delivered at 10-15 Hz in 12 trials and at 15-20 Hz in one (Rettwitz-Volk 1998).

The three criteria used to define a high volume strategy (HVS) with HFOV are given in the objectives. All 15 trials with a HVS used a higher mean airway pressure (MAP) on HFOV than on CV. In addition, two trials (Thome 1998; Moriette 2001) used both alveolar recruitment manoeuvres and weaning of FiO2 prior to weaning MAP, while three other trials (Gersmann 1996; Clark 1992; Van Reempts 2003) used weaning of FiO2 first and Ogawa et al (Ogawa 1993) used alveolar recruitment manoeuvres. In six trials lung volume recruitment aimed at weaning the FiO2 to 0.30 or less (Gersmann 1996; Thome 1998; Johnson 2002; Vento 2005; Dani 2006; Lista 2008), whereas in the other trials the targeted FiO2 was higher than 0.30 or not specified. Two trials (HIFI 1989; Rettwitz-Volk 1998) did not use a HVS for HFOV.

In all trials, CV was administered using time cycled, pressure limited ventilators. There was a large variation in the specific methods of administration of CV that might provide lung protection. Details are given in the Table of Included Studies.

Surfactant therapy with animal derived extracts was used as therapy for RDS in the majority of participants in all but two trials (HIFI 1989; Clark 1992).

Postnatal corticosteroids for CLD were used in 41 - 61% of infants in three trials (Gersmann 1996; Thome 1998; Courtney 2002), in 20% of infants in one trial (Gerstmann 1996) and in less than 8% of infants in two trials (Moriette 2001; Van Reempts 2003). Plavka et al (Plavka 1999) reported cumulative dosage and Courtney et al (Courtney 2002) reported mean days of therapy in infants in each group. In all studies, the usage of postnatal steroids was similar in the two treatment groups. In the Vento trial (Vento 2005), corticosteroids were administered to 35% of survivors in the HFOV group and to 60% of survivors in the CV group.

In the Durand-Courtney trial (Durand 2001 and Courtney 2002) prophylactic indomethacin was given routinely to all infants.

Outcomes

Not all outcomes were reported in each study. The definitions of CLD 'at 28 days' differed between studies. CLD was assessed at 28 days of age in six studies (HIFI 1989; Ogasawara 1991; Rettwitz-Volk 1998; Thome 1998; Moriette 2001; Van Reempts 2003; Schreiber 2003) and 30 days of age in the other two (Clark 1992; Gersmann 1996). In five studies, the definition of CLD at 28 days of age was based on oxygen therapy alone (Rettwitz-Volk 1998; Thome 1998; Plavka 1999; Moriette 2001; Schreiber 2003), while in the remainder both oxygen therapy and an abnormal chest x-ray were required.

'Late' CLD at term equivalent age varied from 36 weeks PMA (Clark 1992; Thome 1998; Plavka 1999; Moriette 2001; Courtney 2002; Johnson 2002) to 'at discharge' (Gersmann 1996) [mean PMA 37.1 (36.5, 37.9) weeks in HFOV group and 37.5 (36.6, 38.0) weeks in CV group]. The criteria for CLD at term equivalent age was based on use of oxygen therapy in nine trials, on clinical score (oxygen plus signs) in one trial (Plavka 1999), on oxygen or use of assisted ventilation in two trials (Courtney 2002; Van Reempts 2003) and on oxygen use plus an abnormal chest radiograph in one trial (Schreiber 2003).

In each trial, cross-over to the other treatment was allowed when pre-determined failure criteria were reached. These criteria (hypoxaemia and/or hypercarbia) were similar in each trial and for each treatment group, but the decision to cross over was left to the clinician. In two trials (Clark 1992; Rettwitz-Volk 1998), the additional criterion for cross-over of severe pulmonary interstitial emphysema was applied only to the CV group. Because of the variable definition of 'failure of assigned treatment' between treatment groups, this outcome has not been included in the meta-analysis. When cross-over occurred, the subjects were analysed in the groups as randomised.
Risk of bias in included studies

Details of the methodological quality of each study are available in the table Characteristics of Included Studies.

Randomisation: there were adequate efforts to conceal treatment assignment in each study.

Blinding of treatment: not possible in any study.

Exclusions after randomisation: minimal for primary outcomes (all less than 8%).

Blinding of outcome assessment: variable between outcomes and studies. Assessment of chest x-rays for the diagnosis of CLD was blinded as to treatment group in 5 studies. (Clark 1992; Ogawa 1993; Plavka 1999; and Moriette 2001; Schreiber 2003) Blinded head ultrasound assessments were carried out in 9 trials. (HIFI 1989; Clark 1992; Ogawa 1993; Moriette 2001; Sonwend 2001; Courtney 2002; Johnson 2002; Van Reempts 2003 and Schreiber 2003)

EFFECTS OF INTERVENTIONS

Seventeen trials involving 3652 infants were included.

1. Mortality

There were no significant differences in the rates of mortality by 28 - 30 days [Outcome 1.1, 2060 infants in nine trials, summary RR 1.09 (95% CI 0.88, 1.35)] or in the rates of mortality by 36 - 37 weeks PMA or discharge [Outcome 1.6, 2885 infants in 15 trials, summary RR 0.98 (95% CI 0.83, 1.14)], either in any individual trial or in the overall analyses. Subgroup analyses including use of volume recruitment on HFOV, routine use of surfactant, use of piston oscillators, use of lung protective strategies on CV and inspiratory:expiratory ratio on HFOV also failed to show any significant differences in mortality rates.

Mortality by 28-30 days:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFOV</th>
<th>CV</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark 1992</td>
<td>7</td>
<td>37</td>
<td>5</td>
<td>28</td>
<td>4.1%</td>
</tr>
<tr>
<td>Gerstmann 1996</td>
<td>0</td>
<td>64</td>
<td>2</td>
<td>61</td>
<td>1.9%</td>
</tr>
<tr>
<td>HIFI 1989</td>
<td>60</td>
<td>327</td>
<td>60</td>
<td>346</td>
<td>42.3%</td>
</tr>
<tr>
<td>Moriette 2001</td>
<td>28</td>
<td>139</td>
<td>24</td>
<td>134</td>
<td>17.7%</td>
</tr>
<tr>
<td>Ogawa 1993</td>
<td>0</td>
<td>46</td>
<td>1</td>
<td>46</td>
<td>1.1%</td>
</tr>
<tr>
<td>Plavka 1999</td>
<td>2</td>
<td>21</td>
<td>2</td>
<td>20</td>
<td>1.5%</td>
</tr>
<tr>
<td>Schreiber 2003</td>
<td>17</td>
<td>102</td>
<td>15</td>
<td>105</td>
<td>10.7%</td>
</tr>
<tr>
<td>Thome 1998</td>
<td>10</td>
<td>140</td>
<td>11</td>
<td>144</td>
<td>7.9%</td>
</tr>
<tr>
<td>Van Reempts 2003</td>
<td>24</td>
<td>147</td>
<td>18</td>
<td>153</td>
<td>12.8%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1023</td>
<td>1037</td>
<td>100.0%</td>
<td>1.09 [0.88, 1.35]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>148</td>
<td>138</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Cib = 2.76, df = 8 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)
2. Chronic lung disease at 28-30 days

The use of oxygen therapy at 28 - 30 days was reported for 1043 infants in six trials. There was no significant difference between the HFOV and CV groups in the individual trials, or in the meta-analysis [Outcome 1.3, summary RR 0.98 (95% CI 0.88, 1.10)].

CLD in survivors at 28-30 days of age, based on the use of oxygen or mechanical ventilation and the presence of an abnormal chest x-ray, was reported for 820 infants in four trials (Outcome 1.4). Two trials (Clark 1992; Gerstmann 1996) showed a significantly lower incidence of this outcome in the HFOV group and there was a trend towards a reduced incidence in the overall analysis [summary RR 0.86 (95% CI 0.74, 1.01)]. This latter meta-analysis showed significant heterogeneity ($I^2 = 71.3\%$ ) and when a random effects model was used the summary RR is 0.66 (95% CI 0.41, 1.07).

Five trials involving 1160 infants reported both mortality and CLD at 28 - 30 days (Outcome 1.5). Two showed a significant decrease of this combined outcome in the HFOV group (Clark 1992; Gerstmann 1996). In the overall analysis, there was a non-significant trend towards a reduced risk of 'death or CLD at 28-30 days' in the HFOV group [summary RR 0.94 (95% CI 0.85, 1.04)].
3. CLD at 36 - 37 weeks postmenstrual age (PMA) in survivors

CLD in survivors at 36 - 37 weeks PMA or at discharge was reported for 2369 infants in 15 trials (Outcome 1.7). Four trials (Clark 1992; Gerstmann 1996; Durand 2001; Vento 2005) found a significant decrease in the HFOV group. In the overall analysis using a fixed effects model, there was a reduction of CLD in the HFOV group [summary RR 0.89 (95% CI 0.81, 0.99), RD 0.04 (95% CI -0.08, -0.01)] of borderline significance. There was significant heterogeneity in this meta-analysis ($I^2 = 57\%$) and using a random effects model gave a summary RR of 0.85 (95% CI 0.70, 1.04), which is not significant.

### Subgroup analyses

The subgroup analysis by high volume strategy (HVS) on HFOV (Outcome 2.2) showed similar results in the subgroups "HVS with target FiO2 < 0.30" [6 trials, 1066 infants, summary RR 0.93 (95% CI 0.81, 1.06)] and "HFV with target FiO2 > 0.30 or unspecified" [8 trials, 1216 infants, summary RR 0.86 (95% CI 0.73, 1.00)]. Only one trial not using HVS reported CLD and had no cases of CLD to contribute to the overall analysis.
In the subgroup analysis by use of routine surfactant, (Outcome 3.2) only one small trial of 51 infants \(^{(Clark 1992)}\) reporting CLD at 36 weeks did not use surfactant. This trial showed a significant reduction in the HFOV group \([RR 0.23 (95\% CI 0.07, 0.73)]\). This result was significantly different from the subgroup analysis of the 14 trials involving 2318 infants in which surfactant was used. The latter result is similar to the overall analysis of CLD at 36 weeks PMA \([summary fixed effects RR 0.91 (95\% CI 0.82, 1.01)]\) with persisting heterogeneity \((I^2 = 51\%)\).

Subgroups by use of different types of oscillator (flow interrupters, true piston oscillators or both) showed no statistical difference (overlapping 95% confidence intervals) between the summary RRs of the subgroups (Outcome 4.2). For the subgroup of 10 trials of 1407 infants that used of HF piston oscillators (including the Van Reempts trial, where 83% of study patients were ventilated with an HF oscillator and 17% were ventilated with a flow interruptor), there was a significant reduction in CLD in the HFOV group \([summary RR 0.82 (95\% CI 0.70, 0.95), RD -0.06 (95\% CI -0.11, -0.02), NNT 17 (95\% CI 9, 50)]\). Using the 99% CI, the result was of borderline significance \([summary RR 0.82 (99\%CI 0.67, 1.00)]\). There was significant heterogeneity \((I^2 = 65\%)\). Using a random effects model, the RR was not significantly reduced \([summary RR 0.76 (95\% CI 0.55, 1.03) (99\% CI 0.50, 1.14)]\).
For the subgroup analysis based on lung protective strategies (LPS) on CV (Outcome 5.2), the outcome was borderline different between the groups "definitely LPVS" and "definitely no LPVS" with 95% confidence intervals marginally overlapping, showing a larger and statistically significant benefit in the subgroup "definitely no LPVS" [fixed effect summary RR 0.48 (95% CI 0.31, 0.75), RD -0.24 (95 CI -0.37, -0.10), NNT 4 (95% CI 4, 10)]. There was heterogeneity in both subgroups, however \( I^2 = 51\% \) and 54\% respectively. Using a random effects model, the reduction in risk of CLD was not statistically significant in the "definitely no LPVS"-subgroup [random effects summary RR 0.84 (95% CI 0.91, 1.02)] and not different from the effect in the "definitely LPVS"-subgroup [random effects summary RR 0.84 (95% CI 0.59, 1.20)]
Subgroups by age at randomisation (less than 2 hrs, 2 - 6 hrs, greater than 6 hrs) showed no statistical difference (overlapping 95% confidence intervals) between the summary RRs of the subgroups (Outcome 6.2). The group of four trials of 782 surviving infants who were randomised at two to six hours of age showed a significant overall reduction in the risk of CLD with minimal heterogeneity [summary RR 0.72 (95% CI 0.59, 0.87), (99% CI 0.56, 0.92), I² =23%).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFOV</th>
<th>CV</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>5.2.1 Definitive LPS on CV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courtney 2002</td>
<td>70</td>
<td>201</td>
<td>93</td>
<td>210</td>
</tr>
<tr>
<td>Dani 2006</td>
<td>4</td>
<td>11</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Durand 2001</td>
<td>5</td>
<td>19</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Lista 2008</td>
<td>2</td>
<td>18</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Thome 1998</td>
<td>32</td>
<td>126</td>
<td>30</td>
<td>129</td>
</tr>
<tr>
<td>Van Reempts 2003</td>
<td>24</td>
<td>122</td>
<td>19</td>
<td>133</td>
</tr>
<tr>
<td>Vento 2005</td>
<td>2</td>
<td>19</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>516</td>
<td>540</td>
<td>36.4%</td>
<td>0.86 [0.71, 1.03]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>139</td>
<td></td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 12.15, df = 6 (P = 0.06); I² = 51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.64 (P = 0.10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **5.2.2 Probable LPS on CV**  |
| Craft 2003        | 13 | 19  | 13 | 21  | 2.7%  | 1.11 [0.70, 1.74] |
| Johnson 2002      | 165| 300 | 163| 292 | 36.3% | 0.99 [0.85, 1.14] |
| Moriette 2001     | 24 | 108 | 30 | 107 | 6.6%  | 0.79 [0.50, 1.26] |
| **Subtotal (95% CI)** | 427 | 420 | 45.6% | 0.86 [0.84, 1.16] |
| **Total events** | 202 |     | 206 |     |
| Heterogeneity: Ch² = 1.11, df = 2 (P = 0.57); I² = 0% |
| Test for overall effect: Z = 0.53 (P = 0.60) |

| **5.2.3 Probably no LPS on CV**  |
| Plavka 1999       | 3  | 19  | 8  | 18  | 1.8%  | 0.36 [0.11, 1.13] |
| Rottwitz-Volk 1998| 0  | 41  | 0  | 46  | Not estimable |
| Schreiber 2003    | 43 | 84  | 34 | 84  | 7.5%  | 1.26 [0.91, 1.76] |
| **Subtotal (95% CI)** | 144 | 148 | 9.3%  | 1.09 [0.79, 1.49] |
| **Total events** | 46  |     | 42  |     |
| Heterogeneity: Ch² = 4.36, df = 1 (P = 0.04); I² = 77% |
| Test for overall effect: Z = 0.52 (P = 0.60) |

| **5.2.4 Definitely no LPS on CV**  |
| Clark 1992        | 17 | 64  | 27 | 59  | 6.2%  | 0.58 [0.35, 0.95] |
| Gerstmann 1996    | 93 | 81  | 81 | 81  | 8.7%  | 0.48 [0.31, 0.75] |
| **Subtotal (95% CI)** | 1180 | 1189 | 100.0% | 0.89 [0.81, 0.99] |
| **Total events** | 407 |     | 454 |     |
| Heterogeneity: Ch² = 30.08, df = 13 (P = 0.005); I² = 67% |
| Test for overall effect: Z = 2.15 (P = 0.03) |
6.2.1 Less than 2 hours

- Dani 2006
- Johnson 2002
- Lista 2008
- Plavka 1999
- Rettwitz-Volk 1998
- Thome 1998
- Vento 2005

Subtotal (95% CI) 534/533 = 1.00 (0.83, 1.09)

Total events: 208/214

Heterogeneity: Chi² = 7.30, df = 5 (P = 0.20); I² = 31%
Test for overall effect: Z = 0.70 (P = 0.48)

6.2.2 2 to 6 hours

- Courtney 2002
- Durand 2001
- Gerstmann 1996
- Moriette 2001

Subtotal (95% CI) 392/396 = 0.98 (0.59, 0.87)

Total events: 116/164

Heterogeneity: Chi² = 3.91, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 3.40 (P = 0.0007)

6.2.3 Greater than 6 hours

- Clark 1992
- Schreiber 2003

Subtotal (95% CI) 113/106 = 1.06 (0.74, 1.37)

Total events: 46/44

Heterogeneity: Chi² = 8.07, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.03 (P = 0.98)

Total (95% CI) 1039/1035 = 1.00 (0.78, 0.96)

Total events: 370/422

Heterogeneity: Chi² = 27.41, df = 11 (P = 0.004); I² = 60%
Test for overall effect: Z = 2.64 (P = 0.008)

Subgroups by inspiratory:expiratory time ratio on HFOV (I:E = 1:1, 1:2 or variable / unknown) showed no statistical difference (overlapping 95% confidence intervals) between the summary RRs of the subgroups (Outcome 7.2). The group of 8 trials of 1105 surviving infants who were given HFOV using an I:E of 1:2 showed a significant overall reduction at the 95% confidence level in the risk of CLD with considerable heterogeneity [fixed effects summary RR 0.82 (95% CI 0.70, 0.86)], but not at the 99% confidence level (99% CI 0.66, 1.02), I² = 69%. The random effects summary RR (0.74) was not significantly reduced in the HFOV group (95% CI 0.51, 1.06)(99% CI 0.46, 1.19).

4. Death or CLD at 36 weeks postmenstrual age

There was a small reduction of the risk of the combined outcome of ‘death or CLD at 36-37 weeks PMA or discharge’ in the HFOV group [Outcome 1.8, summary RR 0.93 (95% CI 0.86, 1.00)] which is of borderline significance using the fixed effects model. In view of moderate heterogeneity (I² = 50%), a random effects model was also used, yielding a nonsignificant difference in the summary RR [0.90 (95% CI 0.78, 1.03)].
Subgroup analyses

There was no statistically significant difference in death or CLD at 36 weeks postmenstrual age between the different categories within each of the subgroups (95% CIs overlap). Within subgroups, some individual categories show significant effects and these are outlined below.

As for the outcome CLD alone, there was a borderline significant overall reduction in death or CLD in the subgroup of trials using true piston oscillators [fixed effects summary RR 0.88 (95% CI 0.79, 0.99), RD -0.05 (95% CI -0.10, 0.00), NNT 20 (95% CI 10, ∞)]. However, there was a persisting moderate heterogeneity (I² = 56.8%). Using a random effects model, the difference was not statistically significant [random effects summary RR 0.84 (95% CI 0.69, 1.04)].

In the subgroup of two trials of 190 infants with no lung protective strategy on CV, there was a significant reduction of death or CLD with HFOV [summary RR 0.56 (95% CI 0.38, 0.81), summary RD -0.22 (95% CI -0.36, -0.09), NNT 5 (95% CI 3, 11), I² =0%].

In the subgroup analysis of age at randomisation, in the group of four trials of 944 infants with randomisation occurring at two to six hours of age there was a significant reduction in death or CLD with HFOV [summary RR 0.79 (95% CI 0.68, 0.91), summary RD -0.10 (95% CI -0.17, -0.04), NNT 10 (6, 25)] with nonsignificant heterogeneity (I² =34.5%). The summary RR remains significantly reduced when the 99% CI was used (99% CI 0.65, 0.95).

In the subgroup of six trials involving 984 infants that used an I:E of 1:2 for HFOV, there was a significant reduction of death or CLD in the HFOV group [summary RR 0.87 (95% CI 0.77, 0.98, RD -0.06, (95% CI -0.11, -0.01), NNT 17 (95%CI 9, 100), I² + 67.1%]. This difference was not significant using a random effects model [summary RR 0.81 (95% CI 0.63, 1.04)].

5. Duration of oxygen therapy

The duration of oxygen therapy was reported in nine trials. The statistical reporting of this outcome differed substantially between trials so meta-analysis was not undertaken.
Gerstmann et al. (Gerstmann 1996) found no significant difference in the duration of oxygen therapy in infants with birth weights of one kilogram or less, but a shorter duration of oxygen therapy in HFOV infants with birth weights over one kilogram [median days (95% CI), 13.2 (6.6, 24.3) vs. 27.6 (14.3, 37.7), \( P = < 0.05 \)]. Two studies reported mean and standard deviations for days of oxygen that were similar in the two groups: Van Reempts et al. (Van Reempts 2003) [HFOV 23.6 (28.2) vs. CV 22.7 (28.5)] and Dani et al. (Dani 2006) [HFOV 20.3 (14.6) vs. CV 22.0 (15.9)].

No significant difference in the median days of oxygen therapy between treatment groups was found in the three other studies \[36 vs. 39.5; (Thome 1998) 20 (95% CI 1, 86) vs. 29 (95% CI 4, 107); (Plavka 1999) 22 (IQR 47) vs. 22 (IQR 41) (Moriette 2001)\]. Craft et al. (Craft 2003) reported mean (and range) for days of oxygen therapy for the two subgroups by birthweight; 500 - 750 g, HFOV 75.5 (1 - 119) vs. CV 53.0 (27 - 93). These differences were not statistically different. Vento et al. (Vento 2005) reported the mean (SD) hours of oxygen therapy that was significantly lower in the HFOV group \[760 (473) \] compared with the CV group \[1445 (1297)\], \( P = 0.03 \). Lista et al. (Lista 2008), finally, reported a significantly longer duration of oxygen dependency in the HFOV group [mean days (standard deviation) in HFOV group 36 (23) and in CV group 19 (11)].

6. Use of mechanical ventilation

The use of mechanical ventilation at 28 - 30 days was reported in three studies and was not significantly different in individual trials or in the meta-analysis.

Nine trials reported the total duration of mechanical ventilation (MV). Overall, the trend was for shorter durations of ventilation in the HFOV groups, but no individual trials showed a significant difference. These data have not been combined in meta-analysis because of differences in the statistical reporting between trials.

In the Provo trial (Gerstmann 1996) the median (95% confidence intervals) days on MV in those with a birth weight less than 1 kg was 24.7 days (95% CI 3.7, 61.4) in the HFOV group and 53.7 days (95% CI 28.4, 103) in the CV group, a trend that was not significantly different. In this trial, there was also a similar median duration of MV in infants with birth weights over 1 kg \[4.1 days (1.7, 6)\] in the HFOV group vs. \[4.5 days (95% CI 3.6, 6.1)\] in the CV group. Clark et al. (Clark 1992) reported medians and ranges for the days on MV for all infants entered in the study that were not significantly different between the HFOV group \[16 days (95% CI 1.8, 67)\] and the CV group \[30.3 days (0.5, 222)\]. Ogawa et al. (Ogawa 1993) reported similar mean (+/- SD) days of mechanical ventilation in the HFOV group \[17.3 +/- 24.4\] and CV group \[13.5 +/- 21\]. Pivak et al. (Pivak 1999) reported means with 95% confidence intervals for duration of mechanical ventilation and no difference between HFOV and CV groups \[5 (95% CI 1, 70)\] vs. \[7 (95% CI 3, 52)\] was shown. Moriette et al. (Moriette 2007) found similar mean (interquartile range, IQR) duration of mechanical ventilation between HFOV and CV groups \[9 (17) vs. 9 (16)\]. Van reempts et al. (Van Reempts 2003) reported similar mean and standard deviations of days of MV in the two groups \[HFOV 7.7 (9.7) vs. CV 4.9 (9.1)\]. Craft et al. (Craft 2003) reported mean (and range) for days of mechanical ventilation for the two subgroups by birthweight; 500 - 750 g, HFOV 43.3 (1 - 136) vs. CV 59 (3 - 133); 751 - 1000 g, HFOV 37.7 (1 - 83) vs. CV 20.1 (1 - 56). These differences were not statistically different. Vento et al. (Vento 2005) reported the mean (SD) hours of mechanical ventilation that were not significantly different between the HFOV group, 310 (313) and the CV group, 656 (981), \( P = 0.15 \). Two trials (Van Reempts 2003; Lista 2008) showed no significant differences in mean days (+ standard deviation) of mechanical ventilation between the HFOV group and the CV group: 4.1 (1.1) vs. 4.5 (2.2) (Van Reempts 2003) and 9.6 (4) vs. 10 (2) (Lista 2008).

7. Failed treatment
Two trials reported failure to maintain gas exchange with the allocated treatment. Thome et al. (Thome 1998) reported a non-significant trend towards more infants failing based on oxygenation index criteria in the HFOV group (7/140 vs. 4/144), while Gerstmann (Gerstmann 1996) reported more failures with CV (1/64 vs. 9/64, P = 0.008).

Six trials reported crossover to the alternate treatment, a decision that was left to the judgement of individual clinicians. In the HIFI trial (HIFI 1989) there was a significant increase of treatment failures (failure to maintain adequate gas exchange) in the HFOV group leading to crossover of treatment (85/346 in the HFOV group and 60/327 in the CV group, P = 0.01). Moriette et al. (Moriette 2001) reported a switch in ventilator mode for fewer infants assigned to HFOV than to CV (15% vs. 29%; OR 0.43 (95% CI 0.24, 0.78)). The UKOS trial (Johnson 2002) found the same rate of failure of assigned treatment (10% in each group), while Courtney et al. (Courtney 2002) reported that more infants exited the assigned mode of treatment in the CV group compared to the HFOV group (52/254 vs. 31/244 respectively, P = 0.02). Van reempts et al. (Van reempts 2003) reported 17 (11.6%) failures in the HFOV group and seven infants crossed over from CV at the discretion of clinicians. In the SyFi trial (Craft 2003), one infant crossed over from HIFI and none crossed over from SIMV.

These data have not been combined in a meta-analysis as there were differences in definitions between trials and possibly in clinician uptake of the option to cross over.

Two trials had the additional failure criterion of PIE in the CV group. These trials reported crossover to be similar between groups (8/46 vs. 9/50) or to be more common in the CV group (5/30 vs. 29%; OR 0.43 (95% CI 0.24, 0.78)).

8. Pulmonary air leak syndromes

Twelve trials involving 2766 infants reported ‘any pulmonary air leak’ (Outcome 1.9). Two trials showed a significant increase in any air leak in the HFOV group [RR 1.38 (95% CI 1.01, 1.89); (Thome 1998) RR 1.67 (95% CI 1.15, 2.43)] (Schreiber 2003). Overall analysis of the twelve trials shows a small but significant increase in the HFOV group [summary RR 1.19 (95% CI 1.05, 1.34), RD 0.05 (95% CI 0.01, 0.08), NNH 20 (95% CI 100, 12].

Gross pulmonary air leak (excluding PIE alone) is reported for 1829 infants in ten trials (Outcome 1.10). No individual trial showed a difference, but overall there is a non-significant
trend towards an increased risk in the HFOV group with no heterogeneity [summary RR 1.30 (95% CI 0.99, 1.70), I² = 0%].

### Subgroup analyses of gross pulmonary air leak

In the subgroup analysis by high lung volume strategy on HFOV, the summary RR gradually shifts from 1.70 (95% CI 0.90, 3.22) for the "HVS with target FiO₂ < 0.30" group towards 0.65 (95% CI 0.17, 2.58) for the "no HVS" group, but the difference was not significant (overlapping 95% CI). There was no significant difference in risk of gross pulmonary air leak between HFOV and CV in none of the subgroups, and no difference in effect between the subgroups. (Outcome 2.4).

### Intraventricular haemorrhage (IVH)

Eleven trials involving 2996 infants reported all grades of IVH (Outcome 1.11). There was no significant difference in the rate of IVH of all grades between the treatment groups in individual trials or in the overall analysis [summary RR 1.05 (95% CI 0.96, 1.15)].

Sixteen trials involving 3625 infants reported the rates of the more severe grades of IVH, Grade 3 or 4 (Outcome 1.12, subgroup). Two trials reported significantly higher rates in the...
HFOV group; the large HIFI study (HIFI 1989), which contributed most weight in the overall analysis [RR 1.41 (95% CI 1.06, 1.88)], and the trial by Moriette et al (Moriette 2001) [RR 1.73 (95% CI 1.04, 2.87)]. Moriette et al (Moriette 2001) reported an increased rate of severe IVH in the HFOV group, both in infants born at less than 28 weeks gestation (HFOV 26/81 vs. CV 15/72) and in infants born at 28 or 29 weeks gestation (HFOV 8/58 vs. CV 4/61). Overall, there was no significant difference in the rates of more severe grades of IVH between the HFOV and CV groups [summary RR 1.11 (95% CI 0.95, 1.30)].

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFOV Events</th>
<th>CV Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFI 1989</td>
<td>84</td>
<td>327</td>
<td>24.1%</td>
<td>1.41 [1.06, 1.88]</td>
</tr>
<tr>
<td>Clark 1992</td>
<td>7</td>
<td>37</td>
<td>2.7%</td>
<td>0.88 [0.33, 2.34]</td>
</tr>
<tr>
<td>Ogawa 1993</td>
<td>2</td>
<td>46</td>
<td>0.4%</td>
<td>2.00 [0.19, 21.30]</td>
</tr>
<tr>
<td>Gerstmann 1996</td>
<td>2</td>
<td>64</td>
<td>2.4%</td>
<td>0.32 [0.07, 1.51]</td>
</tr>
<tr>
<td>Courtney 2002</td>
<td>45</td>
<td>244</td>
<td>17.4%</td>
<td>1.04 [0.72, 1.51]</td>
</tr>
<tr>
<td>Craft 2003</td>
<td>4</td>
<td>22</td>
<td>1.9%</td>
<td>0.87 [0.27, 2.84]</td>
</tr>
<tr>
<td>Durand 2001</td>
<td>1</td>
<td>24</td>
<td>1.6%</td>
<td>0.25 [0.03, 2.08]</td>
</tr>
<tr>
<td>Johnson 2002</td>
<td>38</td>
<td>400</td>
<td>21.7%</td>
<td>0.69 [0.46, 1.01]</td>
</tr>
<tr>
<td>Moriette 2001</td>
<td>34</td>
<td>139</td>
<td>7.6%</td>
<td>1.73 [1.04, 2.87]</td>
</tr>
<tr>
<td>Plavka 1999</td>
<td>21</td>
<td>21</td>
<td>0.8%</td>
<td>0.96 [0.15, 6.13]</td>
</tr>
<tr>
<td>Rettwitz-Volk 1998</td>
<td>5</td>
<td>46</td>
<td>0.8%</td>
<td>2.72 [0.55, 13.33]</td>
</tr>
<tr>
<td>Schreiber 2003</td>
<td>18</td>
<td>102</td>
<td>5.4%</td>
<td>1.32 [0.70, 2.52]</td>
</tr>
<tr>
<td>Thome 1998</td>
<td>19</td>
<td>140</td>
<td>7.0%</td>
<td>1.09 [0.60, 1.98]</td>
</tr>
<tr>
<td>Van Reempts 2003</td>
<td>14</td>
<td>147</td>
<td>5.0%</td>
<td>1.12 [0.55, 2.30]</td>
</tr>
<tr>
<td>Vento 2005</td>
<td>3</td>
<td>20</td>
<td>0.8%</td>
<td>1.50 [0.28, 8.04]</td>
</tr>
<tr>
<td>Lista 2008</td>
<td>1</td>
<td>19</td>
<td>0.4%</td>
<td>1.11 [0.07, 16.47]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1798 1827 100.0% 1.11 [0.95, 1.30]

Total events 279 296
Heterogeneity: Chi² = 18.15, df = 15 (P = 0.25); P = 17%
Test for overall effect: Z = 1.32 (P = 0.19)

In the subgroup analyses of severe grades 3 or 4 IVH, no statistically significant differences were apparent between any of the categories within the groups. Some individual groups within the subgroup analyses showed increases in the rates of severe IVH. In the subgroup by use of high volume strategy for HFOV (Outcome 2.5), the two trials (HIFI 1989, Rettwitz-Volk 1998) in which HVS was not used showed a significant increase in the risk of severe IVH [summary RR 1.45 (95% CI 1.09, 1.83), RD 0.074 (95% CI 0.02, 0.13), NNH 14 (95% CI 56, 8)]. The RR is of borderline significance when the 99% CI is used (1.00, 2.11). There was a significant increase in the rate of grade 3 or 4 IVH in the subgroup analysis of two trials (HIFI 1989, Clark 1992) not using surfactant replacement therapy [summary RR 1.36 (95% CI 1.03, 1.79), RD 0.07 (95% CI 0.01, 0.13), NNH 15 (95% CI 143, 8)]. Most of the weight in these latter two analyses was contributed by the HIFI trial (HIFI 1989).

10. Periventricular leukomalacia (PVL)

PVL was reported for 3539 infants in 15 studies. There was a nonsignificant trend towards an increased rate with HFOV in the HIFI trial (HIFI 1989) [RR 1.61 (95% CI 0.99, 2.60)], but no significant difference overall [summary RR 1.10 (95% CI 0.85, 1.43)] (Outcome 1.13).
In the subgroup analyses, there were no significant differences between categories within the subgroups (95% CIs overlap).

In the subgroup by use of high volume strategy for HFOV (Outcome 2.6), the two trials in which HVS was not used show a significant increase in the risk of PVL [summary RR 1.64 (95% CI 1.02, 2.04)]. This was not significant at the 99% CI level (0.88, 3.06).

In the subgroup of 2 trials in which lung protective strategies on CV were not used, there was a significant increase in PVL in the HFOV group [RR 1.57 (95% CI 0.99, 2.48)]. This was not significant at the 99% CI level (0.86, 2.86).

Most of the weight in these latter two analyses was contributed by the HIFI trial.

### 11. Retinopathy of prematurity (ROP)

Ten trials with 2364 surviving infants report significant ROP (grade 2 or more) (Outcome 1.14). The overall analysis showed a significant decrease in the HFOV group with no heterogeneity [summary RR of 0.84 (95% CI 0.72, 0.97), RD -0.04 (95% CI -0.07, -0.01), NNT 30 (15, 357), I² = 8%].
12. Pulmonary function tests, symptoms and growth at follow-up

No significant differences in pulmonary function test results were found during the neonatal period (Abbasi 1991) or at discharge (Gerhardt 1989) in subgroups of infants from individual centres in the HIFI trial (HIFI 1989).

Long-term follow-up assessments (in 82% of survivors), including pulmonary function tests (in 43% of survivors from seven of the ten centres), were carried out at nine months corrected age in infants from the HIFI trial (HIFI 1989) (The HIFI Study Group 1990a). There were no significant differences in respiratory function tests (compliance, resistance, lung volumes) or in the incidence of respiratory tract infections, hospital re-admissions, respiratory symptoms and signs (retractions and episodes of wheezing) or in growth.

Twelve month follow-up of patients in the Ogawa trial (Ogawa 1993) trial showed persistence of abnormal fibrous or emphysematous shadows on chest x-ray in two of the infants in the HFOV group and four in the CV group.

Eighty seven percent of the infants in the Provo trial (Gerstmann 1996) were followed up at a mean age of 6.4 years. Improved respiratory function tests (decreased peak expiratory flow, increased residual lung volume, maldistribution of ventilation) were found in the HFOV group, but there were no significant differences in symptoms (pulmonary illness, asthma, hospitalisation) between the groups.

Of 185 survivors from 12 centres in the UKOS trial (Johnson 2002), 149 were invited for respiratory function tests and these were successfully carried out in 76 at 11 - 14 months of age (Thomas 2004). No differences were found between the HFOV and CV groups in any of the measures (functional residual capacity, inspiratory and expiratory resistance, respirator rate). Respiratory symptoms, treatments and growth were assessed at two years of age (Marlow 2006) and there were no differences between the HFOV and CV groups.

A two years of age assessment of 138 (82%) of survivors in the NOVA study (Schreiber 2003) - re-analysed by type of ventilation) revealed no difference in the mean height, weight or head circumference between the HFOV and CV groups.

13. Neurodevelopmental outcomes at follow up

Neurodevelopmental status at follow-up was reported for seven studies.
The age and methods of assessment varied between studies so the results are presented in the text and not analysed by meta-analysis.

Neurodevelopmental status was assessed at 16 to 24 months corrected age in 77% of survivors of the HIFI study (HIFI 1989) (185 HFOV & 201 CV) using Bayley psychometric tests and central nervous system examinations (The HIFI Study Group 1990b). The rate of moderate to severe abnormality (Bayley's scores more than one SD below the mean or neurological abnormality) was higher in the HFOV group [RR 1.28 (95% CI 1.02, 1.60)]. The rate cerebral palsy was 11% in both groups. There was an increase in the rate of hydrocephalus in the HFOV group [RR 2.08 (95% CI 1.07, 4.06)]. Using logistic regression, abnormal neurological status was shown to be associated with the increased rate of severe grades 3 or 4 IVH in this study.

One year follow-up in the trial by Ogawa et al (Ogawa 1993) showed no significant difference in motor and/or mental development, although the method of neurological assessment was not given.

Gerstmann et al (Gerstmann 1996) reported neurodevelopmental status at a mean of 6.4 years for 87% of the infants. Assessment of mental function, using the Wechsler Scale for Children, and motor function, using the Bruinink-Oseretsky test showed no significant difference in mean scores between the two groups.

Moriette et al (Moriette 2001) assessed neuromotor outcome at the corrected age of two years in 192 of 212 survivors (90%) using a physician questionnaire. Despite a nonsignificant increase in severe IVH rate in the HFOV group as compared with the CV group, the risk of spastic cerebral palsy was significantly lower for infants ventilated with HFOV [4% versus 17%, OR 0.87 (95% CI 0.79, 0.96)], even after adjustment for multiple factors. Survival without cerebral palsy was significantly more likely in the HFOV group than in the CV group [OR 1.89 (95%CI 1.04, 3.44)]. The UKOS trial (Johnson 2002) reported neurodevelopmental outcomes at 22 - 28 months (corrected for prematurity) based paediatric report for 73% of survivors and on parent questionnaires for 49% of survivors. No difference between HFOV and CV groups were found.

Van reempts et al (Van Reempts 2003) followed up a subgroup of infants who were less than 30 weeks gestation or 1250 grams at birth, or had intracranial lesions on ultrasound. This included 70 infants in the HFOV group and 68 in the CV group, representing 57% and 51% respectively of survivors in the whole trial. Bayley motor and mental developmental indices, as well as motor diagnoses, were assessed at seven to twelve months corrected age. There was no significant difference between the groups, with 60% of HFOV infants and 70% of CV infants being completely normal. Follow-up of only the 'abnormal' infants at 18 - 24 months corrected age revealed none of the infants in the HFOV group and four of the infants in the CV group were persistently abnormal, which was not statistically different.

Schreiber et al (Schreiber 2003) re-analysed the follow-up data from the NOVA study according to mode of ventilation. Of the 168 survivors to two years of age (84 in each group), data were available for 66 (78.6%) of those in the HFOV group and 72 (85.7%) in the CV group. Based on blinded assessments using Bayley's Scales (mean scores and number with scores < 70) and Pediatric neurological assessment, there were no differences between the groups.

14. Length of stay and hospital costs

The total hospital costs from a subgroup of patients from one centre in the Provo trial (Gerstmann 1996) suggested that the median hospital costs were less in 42 patients randomised to HFOV.
compared with 41 in the CV group. In this trial, similar differences were found for those infants with birth weights of one kilogram or less and those of more than one kilogram. There were no significant reductions in the median length of hospital stay or in median duration of IPPV in this trial nor in the Rettwitz-Volk and Clark trials, although the trend in each case was towards a reduction in the HFOV group. The UKOS trial reported similar median and range of days hospital stay in survivors between treatment groups (HFOV 94, 73-114; CV 89, 70-112).

15. Other outcomes

Outcomes by birth weight and gestational age have been variably reported in the trials. This important subgroup analysis will be attempted in a future update, following author contributions to an individual patient data analysis that is currently underway (principal investigator Filip Cools).

Use of surfactant was not a prespecified outcome in this review. Three trials reported less use of surfactant in the group receiving HFOV. In four trials there was no significant difference in surfactant use.

DISCUSSION

In this review, the search revealed 17 trials that met prespecified eligibility criteria and five trials that were excluded. It is possible that there are other trials that have not been published or were published in a language not covered by this systematic review. The reviewers would be most interested in hearing of other published, unpublished or ongoing trials.

Limitations of this review

The studies have been carried out over a long time period (20 years) during which changing obstetric and neonatal practices may have influenced the conditions under study such as RDS, IVH and CLD. Participants in early trials could be up to 34 weeks gestational age or 2000 g birth weight, whereas recent trials have been confined to infants of less than 30 weeks gestational age or less than 1200 g birth weight.

Interventions varied by type of ventilator and strategy used for HFOV and CV. Over time it was more likely that HFOV was delivered using a HVS, which would be likely to improve the effect of HFOV, while CV is more likely to be delivered using lung protective strategies, which could reduce the comparative effectiveness of HFOV. In the light of the more recent discussion about the importance of obtaining an "optimal alveolar recruitment" during HVS by aiming at a FiO₂ below 0.30 or even 0.25 during the phase of lung volume recruitment, the subgroup analysis by HFOV strategy was further refined by looking separately at HVS-trials that targeted a FiO₂ < 0.30 and HVS-trials that targeted a FiO₂ > 0.30. However, this subgroup analysis remains to be based on the intended or prescribed ventilation strategy, which might not always reflect the actually used ventilation strategy in the trial. This might be further explored in the individual patient data meta-analysis which is currently under way.

The lung protective strategy on CV to prevent CLD is difficult to define. There are variable maneuvers that principally affect acute lung injury rather than CLD. In this review, four categories were used to evaluate trials that used most strategies ("definite LPS") compared with the other extreme of none ("definitely no LPS") and two intermediate groups. This summary data is based on mixed, soft evidence and might also be able to be explored further in the above mentioned individual patient data meta-analysis.
The quality of the studies was generally high, as all attempted to conceal the randomisation process. However, the interventions were not blinded in any study and this could be associated with bias regarding the use of co-interventions and the ascertainment of outcomes, such as duration of mechanical intervention and oxygen therapy. Ascertainment of outcomes was generally complete or made so by author clarification. Since the treatment could not be blinded in any study, outcomes that were caregiver dependent, such as the duration of oxygen therapy or diagnosis of CLD, may be less valid.

**Pulmonary outcomes**

The overall analysis of CLD at 28 - 30 days is dominated by the HIFI trial (HIFI 1989) trial, which is the largest. Soon after the completion of this study, it was criticized because the methodology used to apply HFOV did not include methods to recruit lung volume (Froese 1991). This criticism is partly supported by the results of subsequent trials that used a high volume strategy where there was a significant reduction in CLD at 28 - 30 days of age (Clark 1992; Gerstmann 1996). The HIFI trial (HIFI 1989) did not report the rates of CLD at term equivalent age or discharge and overall analysis of the remaining trials showed no significant reduction in this outcome with HFOV.

The interventions (treatment and control) varied from trial to trial. Jouvet (Jouvet 1997) found that HFOV generated by a ventilator using flow interruption (e.g. Drager Babylog) was less powerful than HFOV generated by a ventilator using a piston (e.g. Sensormedics), so that there was an inability to increase tidal volume when pressure amplitude was increased above 50%. None of the studies using flow interruption rather than piston oscillation found a difference in the incidence of chronic lung disease.

Although there were no statistically significant differences in the other subgroup analyses of CLD, there were some specific groups of trials which showed a significant reduction in CLD with HFOV. The explanations for this may not be clear. For example, randomisation at 2 - 6 hrs of age compared with 0 - 2 hrs may have included infants with more definite lung disease, rather than a mixed group including those with hypoventilation at birth. Many factors may have been interacting, such as use of antenatal corticosteroids, use of surfactant, use of piston oscillators for HFOV, use of high volume strategy, use of lung protective strategies on CV, and use of inspiratory:expiratory ratio of 1:2. Although there may be biological plausibility for these factors more research is required to clarify the effectiveness of HFOV. The individual patient data review could examine these multiple variables.

Although there were no significant differences in any individual trials, overall, pulmonary air leaks occurred more frequently in the HFOV group.

Other reviews of the evidence of effectiveness of HFV (both oscillation and jet ventilation) also found that CLD was not reduced when HVS was not used for HFV and/or LPS was used on CV (Bollen 2003; Thorne 2005)

**Neurodevelopmental outcomes.**

Increased rates of IVH or PVL occurred in some individual trials but not overall. The pathophysiological factors that might have led to an increased rate of IVH or PVL are not certain. The authors of the HIFI trial (HIFI 1989) suggested that the nearly constant high mean airway pressure during HFOV might restrict venous return, increase intracranial venous pressure, and decrease cerebral blood flow. However, animal studies (Kinsella 1991) and human studies (Laubscher 1996) failed to show these cardiovascular changes. The latter study reported that cardiac output fell when on HFOV. In a single centre involved in the UKOS study (Johnson 2003), echocardiography was carried out in 45 infants (Osborn 2003). Superior vena cava flow was reduced (< 50 ml/kg/min) in more HFOV (48%) than CV (20%) infants, but this difference was not significant. Cambonie et al. (Cambonie 2003) examined the haemodynamic changes during HFOV vs. CV and found no difference in cardiac function but did find a lower
end diastolic velocity and a higher resistance index in the anterior cerebral artery.

The tendency for higher rates of IVH or PVL found in this review in association with failure to use HVS was also shown in two other reviews of the evidence of effectiveness of HFV (both oscillation and jet ventilation) (Bollen 2003; Thome 2005) and in a review of elective jet ventilation vs. CV (Shults 2003). Failure to recruit lung volume and the consequent cardiorespiratory instability has been implicated (Froese 1991). Whether it was one of these mechanisms or just lack of experience with a new technology at the time is difficult to say. The large HIFI trial (HIFI 1989) dominated this analysis.

In five of the seven trials reporting long term neurodevelopmental outcome, no difference was apparent although in some studies there was considerable loss to follow-up. In one trial neuromotor outcome appeared better in the HFOV group, but the results should be interpreted cautiously because of several limitations in the study.

Research questions raised by this review include:

1. Are there differences in pulmonary outcomes and adverse effects by type of ventilator used to generate HFOV? The question would be answered best by a head to head trial of HFOV using a true oscillator vs. a flow interrupter.

2. What is the long-term growth and development of infants treated with HFOV vs. CV? This could be answered by follow-up of infants enrolled in existing trials.

3. Are there differences in the costs compared to benefits of HFOV? One small study (Gentmam 1996) suggested that HFOV reduced costs of care.

4. Despite increasing the number of subgroup analyses in this update of summary data from trials, marked heterogeneity persists. To further explore the comparison of HFOV and CV, a collaborative study is underway to review individual patient data obtained from the trials using a prespecified protocol for analysis. If you have randomised controlled trial data on this topic and wish to join the collaboration, contact Filip Cools (filip.cools@uzbrussel.be).

AUTHORS’ CONCLUSIONS

**Implications for practice**

There is no clear evidence that elective HFOV compared with CV offers important advantages when used as the initial ventilation strategy to treat preterm infants with acute pulmonary dysfunction. There is no evidence of a reduction in death rate. There may be a small reduction in the rate of CLD with HFOV use, but the evidence is weakened by the inconsistency of this effect across trials and is not significant overall. Adverse effects on short term neurological outcomes have been observed in some studies, but these effects are not significant overall. Most trials reporting long-term outcome have not identified any difference.

**Implications for research**

Any future trials on elective HFOV should target those infants who are at most risk of CLD (extremely preterm infants), compare different strategies for generating HFOV, and report important long-term pulmonary and neurodevelopmental outcomes. Economic analysis should also be
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