High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome (Review)

Wunsch H, Mapstone J
High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

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ABSTRACT

Background
High-frequency ventilation is often used to treat patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) but the effect of this treatment on clinical outcomes has not been well established.

Objectives
The objective of this review is to examine the effect of high-frequency ventilation compared with conventional ventilation as a therapy for ALI or ARDS in children (1 to 17 years old) and adults in order to quantify its effect on patient outcome (mortality, morbidity and other relevant outcomes).

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, issue 4, 2002), MEDLINE (1966 to October Week 5, 2002), EMBASE (1980 to Week 51, 2002), World Wide Web (www.controlled-trials.com, ARDS clinical network), and used Cited Reference Search (Web of Science 1988 to 2002, for specific reference lists of articles). We also contacted authors from each included trial, as well as manufacturers of high-frequency ventilators and other researchers in the field.

Selection criteria
Randomized controlled clinical trials of children and adults comparing treatment using high-frequency ventilation with conventional ventilation for patients diagnosed with ALI or ARDS.

Data collection and analysis
Two reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information.
Main results

Two trials met the inclusion criteria for this review. One trial recruited children (including some children less than one year old) (n = 58) and the other recruited adults (n = 148). Both trials used a high-frequency oscillatory ventilator as the intervention and included variable use of lung-volume recruitment strategies. The intervention groups showed a trend towards lower 30 day mortality (children relative risk (RR) 0.83, 95% confidence interval (CI) 0.43 to 1.62; adults RR 0.72, 95% CI 0.50 to 1.03), although neither study showed a statistically significant difference. Similarly, there was no statistically significant difference between the intervention and control groups for 'Total length of ventilator days' (WMD) -2.00, 95% CI -18.36 to 14.36; and WMD 2.00, 95% CI -6.55 to 10.55 for the child and adult trials respectively). The studies used only proxies to measure long-term quality of life. There was a statistically significant reduction in the risk of requiring supplemental oxygen amongst survivors at 30 days in the paediatric study (RR 0.36, 95% CI 0.14 to 0.93).

Authors’ conclusions

There is not enough evidence to conclude whether high-frequency ventilation reduces mortality or long-term morbidity in patients with ALI or ARDS; further trials are needed.

Plain language summary

No significant difference was found in outcomes when comparing high-frequency ventilation with conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

Patients with acute lung injury and acute respiratory distress syndrome continue to have high mortality. One concern has been that normal mechanical ventilation may increase the damage to lungs; high-frequency ventilation may avoid this problem by providing the same oxygen exchange with less injury to the lung tissue. In two studies (58 children, 148 adults), there was no significant difference between the two methods with regard to mortality of patients at 30 days, or the number of days that a ventilator was used. Children treated with high frequency ventilation were less likely to require extra oxygen after 30 days.

Background

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening conditions that affect many patients cared for in intensive care. Although there is disagreement about the exact definitions, criteria that are often used were set forth by the North American-European Consensus Conference in 1994 (Bernard 1994). The criteria for ALI are acute onset of lung injury, diffuse bilateral infiltrates seen upon chest radiography, PaO₂ / FIO₂ less than 300 mm Hg, pulmonary artery occlusion pressure (PAOP) less than 19 mm Hg, or no clinical evidence of congestive heart failure. ARDS is considered a more severe form of ALI, with PaO₂ / FIO₂ less than 200 mm Hg. Accurate estimation of the incidence of ALI or ARDS has been difficult, and has been placed at anywhere from 1.5 to 75 per 100,000 per year, although more recent studies suggest a number closer to 75 per 100,000 is more accurate (Ware 2000).

Patients with ARDS usually have a risk of mortality greater than 30% (Milberg 1995; Abel 1998). There is currently no method of prevention for ALI and ARDS and mechanical ventilation is considered the primary treatment for these patients. Other treatments are used, such as fluid restriction, repositioning of the patient in the prone position, corticosteroids, and inhaled nitric oxide. However, none of these treatments have been convincingly shown to improve outcome (Ware 2000).

Conventional ventilation (CV) strategies seek to maintain tidal volumes that approximate those seen during spontaneous ventilation, or are higher volumes, in order to achieve a normal partial pressure of arterial carbon dioxide and pH. While conventional ventilation does sometimes provide adequate gas exchange, it is associated with high airway pressures and pulmonary air leaks that are thought to induce further lung injury and potentially harm patients.
High-frequency ventilation (HFV) uses respiratory rates more than four times (and up to 250 times) the normal rate, delivering small tidal volumes. It was introduced for the treatment of ALI or ARDS to optimize gas exchange while preventing the further lung injury seen with conventional ventilation. It has been implemented as a treatment in intensive care units, as both an elective and rescue therapy. However, it is currently used without clear evidence as to whether it confers any benefit. Cochrane reviews examining the use of rescue and elective high-frequency ventilation for lung injury in term and pre-term infants have concluded there is insufficient evidence to recommend its use (Bhuta 2002a, Bhuta 2002b; Henderson-Smart 2002). This systematic review examines the evidence for the use of high-frequency ventilation to treat ALI or ARDS in children and adults to improve morbidity and mortality.

OBJECTIVES

The objective of this review is to examine the effect of high-frequency ventilation compared with conventional ventilation as a therapy for ALI or ARDS in children (1 to 17 years old) and adults in order to quantify its effect on patient outcome (mortality, morbidity and other relevant outcomes).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) that compare high-frequency ventilation to conventional ventilation and include at least one of the outcomes of interest.

Types of participants

Children (1 to 17 years old) and adults (18 plus years old). Participants must be diagnosed with acute lung injury or acute respiratory distress syndrome according to the working definitions of the European-American Consensus Conference on ARDS (Bernard 1994), or similar criteria.

Types of interventions

Use of a high-frequency ventilator (greater than 40 breaths per minute), for any length of time, as a therapy after clinical diagnosis of ALI or ARDS.

Types of outcome measures

Primary outcomes

Mortality (Intensive care unit (ICU), hospital, 30 days, 60 plus days).

Secondary outcomes

Total length of mechanical ventilation (high-frequency and conventional combined), length of stay in the intensive care unit, length of hospital stay, any long-term quality of life measurements, any long-term cognitive measurements, cost effectiveness.

Search methods for identification of studies

Trials were identified by searching electronic bibliographic databases, the reference lists of all identified trials, reference lists of relevant systematic reviews and contacting an author of each included trial.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, issue 4, 2002), MEDLINE (1966 to October Week 5, 2002), EMBASE (1980 to Week 51, 2002), World Wide Web (www.controlled-trials.com, ARDS clinical network), and used Cited Reference Search (Web of Science 1988 to 2002, for specific reference lists of articles).

Electronic bibliographic databases searched:

- MEDLINE (1966 to March 2002). For detailed MEDLINE search strategy see Appendix 1.
- Cochrane Controlled Trials Register (January 2002) as MEDLINE.
- ISI Science Citation Index Expanded (1981 to June 2002) for all included trials.
- World wide web (www.controlled-trials.com, ARDS clinical network).

We contacted research departments at companies that make high frequency ventilators for information on any unpublished industry trials.

No language restrictions were applied.

Data collection and analysis

Identifying Trials
Titles and abstracts of the electronic search results were screened by two reviewers. The two reviewers independently selected trials which met the specific inclusion criteria. Any disagreements were resolved through discussion.

Data Extraction
Data extraction was performed independently by the two reviewers. Disagreements about data extracted were resolved through discussion. Authors of trials were contacted for information needed for review that was not available in the published reports. In particular, both J Arnold and S Derdak were contacted to find out if there were any other outcome measures that may have been collected but not included in the published papers. Both confirmed that there were no other outcomes from the trials.

Data extracted included type of randomization used and allocation concealment, blinding, single or multi-centre, size of study, population (children, adults or both), definition of ALI or ARDS used, specifics of respirator settings (including lung-volume recruitment strategies, and the type of high-frequency ventilator used), outcomes of interest, loss to follow-up, and whether or not analysis was performed according to the intention-to-treat principle.

Methodological quality was evaluated according to the methodology described by Schultz 1995. Particular emphasis was placed on 1. concealment of treatment allocation, 2. generation of allocation sequences, 3. Intention-to-treat analysis. No scoring or grading system was used.

Data Analysis
Trials were summarized individually. A decision was made not to pool results, as the two trials involved mutually exclusive groups of patients.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
Six randomized controlled trials were identified using the search methods described above. Two (Arnold 1994; Derdak 2002) were included in the systematic review. Both of the included studies used high frequency oscillatory ventilation (HFOV) and involved use of a lung-volume recruitment strategy. One was a paediatric trial (Arnold 1994), while the other enrolled only adults (Derdak 2002).

Of the four identified trials that were excluded, one was excluded because patients were not randomized on ventilator type (Dobyns 2002), another because patients were used as their own controls (Hurst 1984), the third because the inclusion criteria for ALI or ARDS was too broad (Carlon 1983) and the last because high-frequency ventilation was begun before patients had even developed ALI/ARDS (Hurst 1990).
Due to the limited number of studies eligible for inclusion in the review, reporting (publication) bias was not assessed using a funnel plot.

Risk of bias in included studies
Details of the methodological quality of studies are in the Characteristics of Included Studies Table. Both trials used adequate allocation concealment (A) and employed valid randomisation techniques (Arnold 1994 used a blinded balanced block design and Derdak 2002 used computer randomization). Treatment could not be blinded in any study due to the type of intervention. Post-randomization exclusions occurred in one trial (Arnold 1994) (12/70 randomized). These were a combination of exclusion within eight hours of enrolment (six patients), protocol violations (four patients) and transfer to another institution (two patients).
Neither study was designed as a cross-over trial. However, both Arnold 1994 and Derdak 2002 allowed cross-over of patients to the alternative treatment if they “failed” the original treatment, based on certain physiological variables chosen at the time of study design. Derdak 2002 also allowed treatment with the alternate form of ventilation if the attending physicians felt that additional therapies could be life saving.

Effects of interventions

30 day mortality
Arnold 1994 and Derdak 2002 both examined 30 day mortality. Neither study found a significant difference in 30 day mortality for those patients treated with HFOV versus CV. Arnold 1994 reported a 30 day mortality of 34% (10/29) for HFOV versus 41% (12/29) for CV (relative risk (RR) 0.83, 95% confidence interval (CI) 0.43 to 1.62). Derdak 2002 had a 30 day mortality of 37% (28/75) for HFOV versus 52% (38/73) for CV (RR 0.72, 0.50 to 1.03).

Six month mortality
Only Derdak 2002 examined six month mortality. This study reports a mortality of 47% (35/75) for HFOV versus 59% (43/73) for CV. There was no significant difference found between the two groups (RR 0.79, 95% CI 0.58 to 1.08).
Total ventilator days
Both studies measured the total number of days on a ventilator. Neither study found a significant difference in length of ventilator days between the HFOV and CV groups (Arnold weighted mean difference (WMD) -2.00, 95% CI -13.61 to 9.61; Derdak WMD 2.00, 95% CI -6.55 to 10.55). Arnold 1994 also included a comparison of total ventilator days for survivors at 30 days (WMD -2.00, 95% CI -18.36 to 14.36).

Length of stay
Neither study reported on length of stay.

Long-term quality of life measurements
Neither study used any validated questionnaires to evaluate long-term quality of life. Both studies measured proxies for long-term quality of life; Derdak 2002 examined the percentage of patients alive on mechanical ventilation at 30 days and six months. Derdak et al report patients alive on mechanical ventilation as a percentage of the total number in that arm of the study (those who survived and died), but we have chosen to present them here as a percentage of the survivors only, which is in line with the presentation of data in Arnold 1994. There was no significant difference between the HFOV and CV groups (30 day RR 1.24, 95% CI 0.70 to 2.19; six month RR 0.15, 95% CI 0.01 to 3.04). Arnold 1994 examined the number of survivors requiring supplemental oxygen at 30 days. The study found that those survivors who had received HFOV were statistically less likely to require supplemental oxygen (RR 0.36, 95% CI 0.14 to 0.93).

Long-term cognitive measurements
Neither study reported on long-term cognitive measurements.

Cost effectiveness
Neither study examined cost effectiveness.

Discussion
Findings
Two randomized, controlled trials were identified for inclusion in this systematic review of high-frequency versus conventional ventilation for treatment of acute lung injury and the acute respiratory distress syndrome in children and adults. Neither Derdak 2002 nor Arnold 1994 showed a statistically significant difference in mortality using HFOV, although both showed a trend towards a decrease in 30 day mortality.

The effect of high-frequency oscillatory ventilation on six month mortality, length of mechanical ventilation, need for continued ventilatory support at 30 days and six months all showed trends towards reduction in one or both study, but were not statistically significant. Regarding other outcomes examined in this review, the only difference found in any of the individual analyses was in the paediatric study (Arnold 1994). There was a statistically significant lower need for supplementary oxygen among survivors at 30 days in the group randomized to HFOV versus conventional ventilation, suggesting that there might be some quality of life benefit using HFOV. However, no other measures of quality of life were examined.

Patients in the control arm of Derdak 2002 had a 30 day mortality of 51%. This is in contrast to a recent trial of low tidal volumes for treatment of ARDS where the reported mortality in controls was 39.8% (at 180 days) (ARDS Network 2002), and also other reports of mortality from ARDS (Milberg 1995; Luhr 1999; Bersten 2002). The higher mortality in the study by Derdak et al suggests that the patients enrolled in this trial may have been more severely ill than most ARDS patients.

Limitations
On a number of key areas of design, the two studies are similar: both trials used the same type of high-frequency ventilator (oscillatory), they both used an open lung approach, and both were designed with the option for patients to receive the alternate therapy. However, we chose to report the findings from these trials separately, as the two studies included mutually exclusive groups of patients: one involves only children less than 35 kg and one involves only adults greater than 35 kg. Of note, Arnold reports in a comment on his article that age was significantly associated with outcome (patients greater than five years of age had a significantly increased mortality compared with those patients less than five years) (Arnold 1995).

Although there are many types of high-frequency ventilators, both studies included in this review used high-frequency oscillation ventilation. This is important to note as the results reported may not necessarily be extrapolated to use with other types of high frequency ventilators. The oscillatory ventilator uses reciprocating pumps or diaphragms and in this respect differs from other types of high-frequency ventilators because it provides active expiration (as well as active inspiration) (Krishnam 2000).

We included the trial by Arnold et al. despite the fact that it randomized some infants (21/62, 34%). Our exclusion criteria were chosen because the review was not set up to examine HFV as a treatment for neonatal lung injury (this has been reviewed elsewhere (Bhuta 2002a; Bhuta 2002b; Henderson-Smart 2002). The aim of the Arnold paper was to examine the use of HFOV in children; given that the majority of participants were not infants (mean age was 3.1 and 2.5 for the intervention and control groups respectively), and that the authors specifically stated that they ex-
cluded any infants with former prematurity with residual chronic lung disease, we felt that this study should still be used, as it otherwise met our inclusion criteria. Also of concern in the results of Arnold 1994 is the exclusion of 12/70 patients after randomization. This exclusion means that the analysis was not done using an intention to treat method. We performed a sensitivity analysis using 30 day mortality to address this concern. Since the 12 dropouts were equally split between the 2 treatment groups, the best case favouring HFV would be the survival of all 6 HFV dropouts and the death of all 6 CV dropouts; this yields a mortality of 10/35 (HFV) versus 18/35 (CV) with a non significant RR 0.56 (95% CI 0.30 to 1.03). Similarly, the worst case assumptions for HFV are a tally of 16/35 (HFV) versus 12/35 (CV) with a non significant RR 1.33 (95% CI 0.74 to 2.39). This reinforces the statement by Arnold et al that the principle findings of the study were not altered when follow-up data from these excluded patients were included in analysis (Arnold 1995). The main limitation of this review is the very small number of trials eligible for inclusion. There may be other trials that have not been published which we did not identify during our search and therefore have not been included. These exclusions remain a potential source of bias. The fact that both of the trials that were included also involved small numbers of participants makes it almost impossible to reach any conclusions regarding the efficacy of the intervention. Even if it had been possible to pool the trial data to increase power, the numbers were still too small to reach meaningful conclusions. While 30 day mortality is certainly an outcome of importance, the utility of measuring length of mechanical ventilation as a useful clinical outcome is also questionable.

Other studies
High-frequency ventilation has come in and out of favour over the last twenty years as a treatment for ALI/ARDS. During this time definitions for ALI and ARDS have changed. The American-European Consensus Conference on ARDS (Bernard 1994; Artigas 1998) has provided some guidance to standardize case definitions, but even now not every paper chooses to use these definitions, and comparisons with earlier studies remains problematic. Moreover, identifying clinically the point at which these criteria have been met is always subjective. Recent Cochrane reviews of high-frequency oscillatory ventilation in neonates found either no mortality benefit (elective therapy) or not enough data to support any conclusion (rescue therapy) (Henderson-Smart 2002; Bhuta 2002a). Initial studies in adults completed when HFV was first introduced showed little evidence that HFOV improved outcome, despite the reasoning that the small lung volumes delivered would decrease further damage to the lungs (Carlton 1983; Hurst 1984; Holzapfel 1987; Schuster 1982). A systematic review in 1998 (Herridge 1998) which included non-randomized studies, found that there was too much heterogeneity in study design and that current clinical trials were underpowered. However, the review also suggested that a potential reason why many of the early studies had failed to demonstrate an improvement with HFV was that they did not include a lung-volume recruitment strategy, which could help to keep alveoli open and further minimize damage to the lung. Instead, these early studies tended to focus on minimizing airway pressures. The more recent trials included in this review (Arnold 1994; Derdak 2002) do incorporate lung-volume recruitment strategies, although debate continues as to how best to achieve this goal. A more recent review of high-frequency ventilation for ALI and ARDS (in 2000) concluded that the treatment should be considered "promising but experimental" due to a lack of evidence that it improved important clinical outcomes (Krishnan 2000). The authors of a recent New England Journal of Medicine review article on ARDS (Ware 2000) chose to refer to treatment with HFV only in a list of references of many approaches to ventilation that have not been shown to be beneficial (the reviews were published prior to Derdak et al).

A recent trial demonstrated a marked improvement in mortality from ALI/ARDS using conventional ventilation with lower tidal volumes as compared with traditional tidal volumes (ARDS Network 2002), although the Cochrane Review of the topic found no clear evidence of a difference in mortality (Petrucci 2003). Both of the trials examined in this review compared HFOV to more traditional tidal volume ventilation, which was considered the standard of care at the time the studies were designed. What constitutes "conventional ventilation" for ARDS is now complicated by the recent emphasis on lower tidal volume ventilation and this issue would need to be addressed in any future trial. High-frequency oscillatory ventilation appears to be no worse than conventional ventilation (as defined at the time the study was designed) for treatment of ALI and ARDS. The little data available suggest that there may be some clinical benefit to HFOV; larger trials that incorporate current standard practice for conventional ventilation, and that are powered to detect clinically significant differences in outcome, are still needed before any conclusions can be drawn regarding its relative merits as a treatment option.

Authors' Conclusions
Implications for practice
There is no evidence that high-frequency oscillatory ventilation increases mortality for patients with ALI or ARDS when compared with conventional ventilation. There is not enough evidence to conclude whether high-frequency oscillatory ventilation reduces mortality and improves quality of life for survivors of ALI or ARDS.
Implications for research

A much larger randomized controlled trial of high-frequency oscillatory ventilation is needed to show whether there are any true benefits from the treatment.

As well as focusing on hard outcomes, future trials should assess both quality of life for survivors and cost-effectiveness.

Acknowledgements

We would like to thank Dr. Mathew Zacharias, Prof. Marcus Müller, Prof. Nathan Pace, Prof. Harald Herkner Janet Wale, Nete Villebro and Kathie Godfrey for their help and editorial advice during the preparation of this review.

We would like to thank Dr. Craig Coopersmith for his clinical advice and support.

References

References to studies included in this review

Arnold 1994 (published data only)


Derdak 2002 (published data only (unpublished sought but not used))


References to studies excluded from this review

Carlton 1983 (published data only)


Dobyns 2002 (published data only)


Hurst 1984 (published data only)


Hurst 1990 (published data only)


Additional references

Abel 1998


ARDS Network 2002


Arnold 1995


Artigas 1998

Bernard 1994

Bersten 2002

Bhuta 2002a

Bhuta 2002b

Henderson-Smart 2002

Herridge 1998
Herridge MS, Slutsky AS, Golditz GA. Has high-frequency ventilation been inappropriately discarded in adult acute respiratory distress syndrome? Critical Care Medicine 1998; 26:2073–7. [MEDLINE: 99991151]

Holzapfel 1987

Krishnan 2000

Lahr 1999

Milberg 1995

Petrucci 2003

Schultz 1995

Schuster 1982

Ware 2000

* Indicates the major publication for the study
CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arnold 1994

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre (5 tertiary care paediatric units). Not analysed by intention to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Body weight &lt;35 kg. Acute diffuse lung injury with decreased oxygenation (see criteria in methods section of paper). Excluded: if &lt;40 weeks post-conceptual age or former prematurity with residual chronic lung disease, obstructive airway disease, intractable septic or cardiogenic shock, non-pulmonary terminal diagnosis.</td>
</tr>
<tr>
<td>Interventions</td>
<td>3100 high-frequency oscillatory ventilator (SensorMedics). Initial settings of FIO2: 1.0, frequency of 5 to 10 Hz, mPaw of CV+ (4 to 8) cm H2O, pressure amplitude of oscillation set for “adequate chest wall movement”, bias gas flow 18 L/min. Controls were ventilated with CV (Servo 900C, Siemens; Volar, Hamilton Medical). Target blood gas values were the same as for HFV. Cross-over to the alternate ventilator was required if the patient met certain treatment failure criteria (see paper).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Duration of mechanical ventilation, 30 day survival, supplemental oxygen at 30 days, neurological events on study.</td>
</tr>
<tr>
<td>Notes</td>
<td>12 patients excluded from the analysis due to: exclusion from the study within eight hours of enrolment. (n = 6); protocol violations (n = 4); transferred to other institution (n = 2). Open lung approach to achieve oxygenation targets used. No specific use of lung-volume recruitment manoeuvres.</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Derdak 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre (13 university-affiliated medical centres). Analysis by intention to treat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Age 16+ years. ARDS diagnosed by American-European consensus criteria. Excluded: weight &lt;35 kg, severe COPD or asthma, intractable shock, severe air leak, non-pulmonary terminal diagnosis with an estimated 6 month mortality &gt;50%, FIO2 &gt;0.80 for more than 48 hrs, or participated in another trial for ARDS or septic shock within 30 days.</td>
</tr>
</tbody>
</table>
Derdak 2002  (Continued)

Interventions 3100B high-frequency oscillatory ventilator (SensorMedics). Initial settings of frequency of 5 Hz, mPaw of CV+5, pressure amplitude of oscillation set for “vibration down to level of mid-thigh”. Switched back to CV when FIO2 was 0.50 or less and mPaw was weaned to 24 cm H2O or less with an SaO2 of 88% or more. Controls were ventilated with CV using the pressure control mode with an initial VT (ml/kg) of 6 to 10, RR adjusted for pH greater than 7.15, PEEP of 10, inspiratory time 33%.

Outcomes Survival without need for mechanical ventilation at 30 days from entry to study, six month mortality, need for mechanical ventilation at 30 days and six months.

Notes Designed as an equivalence trial. 9% of the HFOV group and 16% of the CV group received other rescue therapies. Used lung-volume recruitment manoeuvres, although this was not protocolized.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

The authors from both studies were contacted regarding other outcomes that may not have been published. The authors confirmed that no other outcomes were collected.

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlon 1983</td>
<td>Patient population had “acute respiratory failure” from a variety of reasons and included many patients requiring mechanical ventilation who would not necessarily fit modern criteria for ALI or ARDS.</td>
</tr>
<tr>
<td>Dobyns 2002</td>
<td>Randomized on inhaled nitric oxide, not HFV.</td>
</tr>
<tr>
<td>Hurst 1984</td>
<td>Patients served as their own controls. Total of only nine patients randomized.</td>
</tr>
<tr>
<td>Hurst 1990</td>
<td>Patients in the study who received HFOV were only “at risk” of developing ALI/ARDS.</td>
</tr>
</tbody>
</table>
**DATA AND ANALYSES**

Comparison 1. High-frequency ventilation versus conventional ventilation

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 30 day mortality</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 6 month mortality</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 Length of mechanical ventilation</td>
<td>2</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 Length of mechanical ventilation for survivors</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5 Survivors requiring supplemental oxygen at 30 days</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6 Survivors requiring mechanical ventilation at 30 days</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>7 Survivors requiring mechanical ventilation at six months</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 High-frequency ventilation versus conventional ventilation, Outcome 1 30 day mortality.**

Review: High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

Comparison: High-frequency ventilation versus conventional ventilation

Outcome: 1 30 day mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV n/N</th>
<th>CV n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>10/29</td>
<td>12/29</td>
<td></td>
<td>0.83 [ 0.43, 1.62 ]</td>
</tr>
<tr>
<td>Derdak 2002</td>
<td>28/75</td>
<td>38/73</td>
<td></td>
<td>0.72 [ 0.50, 1.03 ]</td>
</tr>
</tbody>
</table>
### Analysis 1.2. Comparison 1 High-frequency ventilation versus conventional ventilation, Outcome 2 6 month mortality.

**Review:** High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

**Comparison:** 1 High-frequency ventilation versus conventional ventilation

**Outcome:** 2 6 month mortality

<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>
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<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
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<tr>
<td>Derdak 2002</td>
<td>35/75</td>
<td>43/73</td>
<td>0.79 [ 0.58, 1.08 ]</td>
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<th>2</th>
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<tr>
<td>Favours treatment</td>
<td>Favours control</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Analysis 1.3. Comparison 1 High-frequency ventilation versus conventional ventilation, Outcome 3 Length of mechanical ventilation.

**Review:** High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

**Comparison:** 1 High-frequency ventilation versus conventional ventilation

**Outcome:** 3 Length of mechanical ventilation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV</th>
<th>CV</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Arnold 1994</td>
<td>29</td>
<td>29</td>
<td>20 (27)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Derdak 2002</td>
<td>75</td>
<td>73</td>
<td>22 (21)</td>
<td>20 (31)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>10</th>
<th>5</th>
<th>0</th>
<th>-5</th>
<th>-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours treatment</td>
<td>Favours control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-0.200 [-1.361, 0.961]

-2.00 [-6.55, 10.55]
### Analysis 1.4. Comparison 1 High-frequency ventilation versus conventional ventilation, Outcome 4 Length of mechanical ventilation for survivors.

Review: High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

Comparison: 1 High-frequency ventilation versus conventional ventilation

Outcome: 4 Length of mechanical ventilation for survivors

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV N</th>
<th>HFOV Mean(SD)</th>
<th>CV N</th>
<th>CV Mean(SD)</th>
<th>Mean Difference</th>
<th>Mean Difference 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>19</td>
<td>27 (31)</td>
<td>17</td>
<td>29 (18)</td>
<td>-2.00</td>
<td>[-18.36, 14.36]</td>
</tr>
</tbody>
</table>

Favours treatment Favours control

### Analysis 1.5. Comparison 1 High-frequency ventilation versus conventional ventilation, Outcome 5 Survivors requiring supplemental oxygen at 30 days.

Review: High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

Comparison: 1 High-frequency ventilation versus conventional ventilation

Outcome: 5 Survivors requiring supplemental oxygen at 30 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV n/N</th>
<th>CV n/N</th>
<th>Risk Ratio</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>4/19</td>
<td>10/17</td>
<td>0.36</td>
<td>0.14, 0.93</td>
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</tbody>
</table>

Favours treatment Favours control
### Analysis 1.6. Comparison I High-frequency ventilation versus conventional ventilation, Outcome 6 Survivors requiring mechanical ventilation at 30 days.

**Review:** High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

**Comparison:** 1 High-frequency ventilation versus conventional ventilation

**Outcome:** 6 Survivors requiring mechanical ventilation at 30 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV n/N</th>
<th>CV n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak 2002</td>
<td>20/47</td>
<td>12/35</td>
<td>1.24 [0.70, 2.19]</td>
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</tbody>
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### Analysis 1.7. Comparison I High-frequency ventilation versus conventional ventilation, Outcome 7 Survivors requiring mechanical ventilation at six months.

**Review:** High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome

**Comparison:** 1 High-frequency ventilation versus conventional ventilation

**Outcome:** 7 Survivors requiring mechanical ventilation at six months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>HFOV n/N</th>
<th>CV n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derdak 2002</td>
<td>0/40</td>
<td>2/30</td>
<td>0.15 [0.01, 3.04]</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1. Search strategy for MEDLINE

Complaint (1 OR 2 OR 3 OR 4 OR 5 OR 6)
1. Respiratory Distress Syndrome
2. ARDS
3. Acute Lung Injury
4. ALI
5. Respiratory Distress Syndrome/
6. Respiratory Distress Syndrome, Adult/
AND

Treatment (1 OR 2 OR 3 OR 4 OR 5)
1. High adj frequency adj3 ventilation
2. High adj frequency oscillat*
3. Jet adj3 ventilation
4. oscillat* adj3 ventilation
5. High Frequency Ventilation (explode)/
AND

Study Design (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10)
1. Clin* adj3 trial*
2. random*
3. study
4. control*
5. randomised controlled trials/
6. Controlled clinical trials/
7. Random allocation/
8. Double-blind method/
10. Prospective studies/
/ denotes a MEDLINE MESH term
HISTORY
Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2004

26 October 2003
New citation required and conclusions have changed
Substantive amendment

CONTRIBUTIONS OF AUTHORS
HW formulated the question and designed the protocol
JM provided comments on the protocol
HW and JM formulated the search strategy
HW and JM independently screened the results and extracted the data

DECLARATIONS OF INTEREST
None known.

NOTES
The authors would like to note that the final review differs slightly from the original published protocol in a few ways:

1. The protocol stated that we would only include English language studies. After discussion with editors, we chose to broaden our inclusion criteria to include all languages to avoid language publication bias.

2. The protocol stated that we would exclude studies involving children less than one year of age. The study by Arnold et al does include children younger than one. The reasons for the inclusion of this study are detailed in the discussion section.

3. The protocol stated that results from studies would be pooled. After discussion with editors and consultation with statisticians, we decided that given the very small number of studies included in the review (two) involving different age groups, that it was not appropriate to pool the results.

INDEX TERMS
Medical Subject Headings (MeSH)
Adolescent; High-Frequency Ventilation [methods]; Randomized Controlled Trials as Topic; Respiration, Artificial [*methods]; Respiratory Distress Syndrome, Adult [*therapy]
MeSH check words
Adult; Child; Child, Preschool; Humans; Infant