High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis

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ABSTRACT
Objective To determine clinical and physiological effects of high frequency oscillation compared with conventional ventilation in patients with acute lung injury/acute respiratory distress syndrome (ARDS).

Design Systematic review and meta-analysis.

Data sources Electronic databases to March 2010, conference proceedings, bibliographies, and primary investigators.

Study selection Randomised controlled trials of high frequency oscillation compared with conventional ventilation in adults or children with acute lung injury/ARDS.

Data selection Three authors independently extracted data on clinical, physiological, and safety outcomes according to a predefined protocol. We contacted investigators of all included studies to clarify methods and obtain additional data. Analyses used random effects models.

Results Eight randomised controlled trials (n=419 patients) were included; almost all patients had ARDS. Methodological quality was good. The ratio of partial pressure of oxygen to inspired fraction of oxygen at 24, 48, and 72 hours was 16-24% higher in patients receiving high frequency oscillation compared with conventional ventilation,19 with extremely small tidal volumes (1-4 ml/kg) and constant lung recruitment. Although low tidal volumes are associated with substantial mortality,12 morbidity,13 and costs,5 mechanical ventilation is usually required for adequate tissue oxygenation6 but might also perpetuate lung injury by overdistending and rupturing healthy alveoli and by triggering a secondary inflammatory response that intensifies lung injury from repeatedly opening and collapsing lung units.7,10 Lung protective ventilation seeks to limit alveolar desaturation,20 recruit non-aerated alveoli, and prevent further alveolar collapse. Although low tidal volumes with11-14 or without15-17 high positive end expiratory pressure can reduce lung injury from ventilation, mortality in patients with ARDS remains high.1,12

High frequency oscillation is an alternative technique of ventilation in which small tidal volumes are delivered at high frequencies (3-15 Hz) with an oscillatory pump.18 High frequency oscillation theoretically meets the goals of a strategy of lung protective ventilation,19 with extremely small tidal volumes (1-4 ml/kg) and constant lung recruitment. Although some centres increasingly use high frequency oscillation in patients with ARDS who do not tolerate conventional mechanical ventilation,20-22 its use other than as a “rescue” treatment remains controversial.23-24 Several observational studies have shown improved oxygenation in patients with refractory hypoxaemia.25-27 An earlier systematic review of randomised controlled trials found only two small trials and could not draw definitive conclusions about the effect of high frequency oscillation on mortality.21 Additional studies have subsequently become available. Furthermore, in the context of current20,30 and future pandemics, there is a pressing need for evidence on the effects of...
potentially life saving interventions for patients with ARDS. Although large randomised trials of high frequency oscillation are under way, they will not be completed for several years. We therefore performed a systematic review and meta-analysis of randomised controlled trials of high frequency oscillation compared with conventional mechanical ventilation for adults and children with acute lung injury and ARDS to determine effects on mortality, other clinical and physiological outcomes, and adverse events.

METHODS
We developed a systematic review protocol with pre-specified criteria for study selection, outcome measurements, and analysis.

Study identification
We used systematic methods to identify published and unpublished randomised controlled trials of high frequency oscillation compared with conventional mechanical ventilation in patients with acute lung injury, ARDS, or other forms of hypoxaemic respiratory failure. To identify all relevant trials, we electronically searched Medline, Embase, CENTRAL and ISI (from inception to March 2010, see appendix 1 on bmj.com); manually searched reference lists from included studies and review articles; searched conference proceedings of the American Thoracic Society (1994-2009), Society of Critical Care Medicine (1994-2010), European Society of Intensive Care Medicine (1994-2009), and American College of Chest Physicians (1994-2009); contacted clinical experts in the specialty; and searched for unpublished and ongoing trials in clinicaltrials.gov and controlled-trials.com. There were no language restrictions.

Study eligibility
Two investigators (SS, MS), not blinded to study authors or results, independently evaluated eligibility of studies and resolved differences by consensus. To be included studies had to enrol adults or children (aged over 4 weeks and over 42 weeks after conception) with acute lung injury or ARDS who were receiving conventional mechanical ventilation; assign patients randomly to two or more groups, including an experimental group that received high frequency oscillation...
Table 2 Details of high frequency oscillation (HFO) and conventional mechanical ventilation (CMV) in trials included in systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Mode</th>
<th>Tidal volume</th>
<th>Adjustment of PEEP (cm H₂O)</th>
<th>Recruitment manoeuvre protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold et al, 1994</td>
<td>Pressure limited</td>
<td>NR</td>
<td>Clinician discretion</td>
<td>No</td>
</tr>
<tr>
<td>Derdak et al, 2002</td>
<td>Pressure control</td>
<td>6-10 ml/kg actual body weight</td>
<td>10-18, by protocol</td>
<td>No</td>
</tr>
<tr>
<td>Shah et al, 2004†</td>
<td>NR</td>
<td>Mean 7-8 ml/kg ideal body weight</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bollen et al, 2005</td>
<td>Pressure control</td>
<td>Mean 8-9 ml/kg ideal body weight</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Papazian et al, 2005</td>
<td>Volume assist control</td>
<td>6 ml/kg ideal body weight</td>
<td>2 above lower inflection point</td>
<td>No</td>
</tr>
<tr>
<td>Samransamruaj-kit et al, 2005</td>
<td>Time cycled or pressure control</td>
<td>6-7 ml/kg ideal body weight</td>
<td>According toARDS Network protocol¹⁵</td>
<td>No</td>
</tr>
<tr>
<td>Demony et al, 2007</td>
<td>Volume assist control</td>
<td>6-7 ml/kg predicted body weight</td>
<td>According toARDS Network protocol¹⁵</td>
<td>No</td>
</tr>
<tr>
<td>Mentzelopoulos et al, 2007†</td>
<td>Volume assist control</td>
<td>6-7 ml/kg predicted body weight</td>
<td>According toARDS Network protocol¹⁵</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ARD=acute respiratory distress syndrome, ΔP=pressure amplitude of oscillation, PaCO₂=partial pressure of arterial carbon dioxide, PaO₂/FiO₂=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, Paw=airway pressure, PEEP=positive end expiratory pressure, Pplat=plateau pressure, NR=not reported.

*Calculated from mean tidal volume and mean ideal body weight on days 1, 2, and 3; tidal volume adjusted according to ARDS Network low tidal volume protocol.¹⁵
†Calculated from mean total tidal volume per kg of ideal body weight on days 1, 2, and 3. General physiological targets were provided, including limitation of peak inspiratory pressure to 40 cm H₂O, but "more detailed ventilation procedures and methods of weaning" were according to standard protocols of the investigating centres.⁴⁹
‡Conference abstracts, with supplementary information provided by primary investigators.

and a control group that received conventional mechanical ventilation; and report any of our primary or secondary outcomes. For analyses of clinical outcomes, we included trials if patients were allocated to high frequency oscillation or conventional mechanical ventilation as the primary ventilation strategy until resolution of acute lung injury or ARDS. We included trials that enrolled both adults and children because we believed that the physiological benefits of lung recruitment and reduction in tidal volume that occur during high frequency oscillation would be similar for both adult and paediatric ARDS.¹⁵-³⁴-³⁶ We also included trials in which a secondary intervention was delivered as part of high frequency oscillation, such as tracheal gas insufflation or recruitment manoeuvres, as some centres apply these in association with high frequency oscillation. We included trials in which the duration of high frequency oscillation was 24 hours or less for physiological outcome analyses but excluded them from analyses of clinical outcomes.

We accepted authors’ definitions of acute lung injury and ARDS. In trials that enrolled patients with other forms of respiratory failure, we stipulated that a minimum of 70% of patients must have acute lung injury or ARDS to meet inclusion criteria. We excluded crossover trials, in which all patients experience treatment and control interventions in random order.

Data extraction and study quality

Three reviewers (SS, MS, JOF) used a standardised spreadsheet to independently abstract data on study methods, details of ventilation strategies, and study outcomes. Disagreements remaining after contact with authors were resolved by consensus.

We abstracted data on methods of randomisation and allocation concealment,³⁷ number of withdrawals after randomisation and losses to follow-up, crossovers between assigned groups, blinding of outcome assessors,³⁸ and early stopping for benefit.³⁹ We summarised the risk of bias for individual studies using a modified version of the Cochrane Collaboration risk of bias instrument.⁴⁰ As blinding of care givers, patients, and family members is impossible in these trials, we determined whether important co-interventions (suctioning, sedation, and paralysis) and use of rescue treatments for refractory respiratory failure (inhaled nitric oxide, prone positioning, steroids, and extracorporeal oxygenation) were standardised or
Table 3 | Additional interventions or rescue treatments and funding in trials of high frequency oscillation and conventional mechanical ventilation included in systematic review

<table>
<thead>
<tr>
<th>High frequency oscillation</th>
<th>Conventional mechanical ventilation</th>
<th>Sedation and paralysis applied equally to both groups</th>
<th>Protocols for ventilator weaning and extubation</th>
<th>Funding$^a$ (industry support)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al$^{55}$ 2004</td>
<td>Nitric oxide, 4/75; prone position, 2/75; high dose steroids, 1/75</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Derdak et al$^{54}$ 2002</td>
<td>Nitric oxide, 8/75; prone position, 3/75; high dose steroids, 4/75</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Samransamruajkit et al$^{54}$ 2005</td>
<td>Nitric oxide, 1/7</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Demory et al$^{55}$ 2007</td>
<td>Prone position for 12 h before HFO in supine position</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mentzelopoulos et al$^{52}$ 2007</td>
<td>Steroids for ARDS, 21/27 patients paralysed</td>
<td>No</td>
<td>CMV</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NR=not reported, ARDS=acute respiratory distress syndrome.
$^a$Industry funding (CareFusion, formerly Sensor Medics) included partial support of study or provision of Sensor Medics 3100B HFO ventilators.
†Conference abstracts, with supplementary information provided by primary investigators.

equally applied in treatment groups. We assessed the quality of evidence for clinical outcomes, including mortality, treatment failure, and adverse events, according to recommendations of the GRADE working group.$^{41}$

We contacted authors of all included trials to request additional data and to clarify methods as necessary.

Outcomes

We considered the following clinical outcomes: hospital or 30 day mortality (primary outcome), six month mortality, duration of mechanical ventilation, ventilator-free days to day 28 or 30, health related quality of life at one year, and treatment failure leading to crossover to the other arm or discontinuation of the study protocol (secondary outcomes). We accepted authors’ definitions of treatment failure, which could include severe oxygenation failure, ventilation failure, hypotension, or barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema). We also considered physiological outcomes measured at 24, 48, and 72 hours after randomisation: oxygenation, measured by the ratio of partial pressure of arterial oxygen ($P_{O2}$) to inspired fraction of oxygen ($FiO2$) ($P_{O2}/FiO2$ ratio); oxygenation index (OI, defined as $100 \times$mean airway pressure$/P_{O2}/FiO2$ ratio); ventilation, measured by partial pressure of carbon dioxide ($P_{CO2}$) and mean air pressure. Finally, we considered adverse events including barotrauma, hypotension, obstruction of endotracheal tube from secretions, and technical complications and equipment failure in patients treated with high frequency oscillation (including unintentional system air leaks and problems with the oscillatory diaphragm, humidifier, and alarm systems).21,42

Whenever possible, we analysed patients according to their randomly assigned group for all clinical and physiological outcomes.

Statistical analysis

We conducted meta-analyses using random effects models in Review Manager (RevMan) 5.0 (Cochrane Collaboration, 2008) and statistical tests of publication bias using the metabias command in Stata 9.2 (2006; StataCorp, College Station, TX). Random effects models incorporate variation both within and between studies and typically provide wider confidence intervals when heterogeneity is present. We reported continuous outcomes using weighted mean difference (a measure of absolute change) or ratio of means (a measure of relative change)44 and binary outcomes as risk ratios. We considered (two sided) $P<0.05$ as significant and reported individual trial and summary results with 95% confidence intervals.

We assessed heterogeneity between studies for each outcome using the I$^2$ measure$^{44,45}$ and used published guidelines for low ($I^2=25-49$%), moderate ($I^2=50-74$%), and high ($I^2=75$%) heterogeneity.$^{45}$

To assess publication bias we examined funnel plots of treatment effect versus study precision and used Begg’s rank correlation test$^{46}$ and a modified Macaskill’s regression test.$^{37}$ Given the low statistical power
of these tests, we assumed a more liberal level of significance (P<0.10) to indicate possible publication bias.

Subgroup analyses

We prespecified subgroup analyses [based on patient’s age (adult v paediatric) and risk of bias of the trial (low v high or unclear)] (see also appendix 2 on bmj.com) to explore potential heterogeneity for the primary outcome of hospital or 30 day mortality and to assess consistency of results between important subgroups. We also conducted a post hoc analysis of the effect of high frequency oscillation by protocol for 6-24 hours a day until predefined criteria for resolution of severe hypoxaemia were met (most patients were treated for at least four days). We assessed whether differences between subgroups were significant using a z test for interaction.

Table 4 | Clinical outcomes and adverse events in trials of high frequency oscillation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No of trials</th>
<th>No of patients</th>
<th>Significance and heterogeneity</th>
<th>Pooled risk ratio (95% CI)</th>
<th>Pooled risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low risk</td>
<td>4</td>
<td>246</td>
<td>P=0.01, I²=0%</td>
<td>0.70 (0.53 to 0.92)</td>
<td>0.95 (0.58 to 1.60)</td>
</tr>
<tr>
<td>Unclear or high risk</td>
<td>2</td>
<td>119</td>
<td>P=0.89, I²=0%</td>
<td>1.04 (0.65 to 1.66)</td>
<td>0.80 (0.44 to 1.43)</td>
</tr>
<tr>
<td>Interaction z test: P=0.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>4</td>
<td>291</td>
<td>P=0.07, I²=8%</td>
<td>0.77 (0.58 to 1.02)</td>
<td>0.80 (0.44 to 1.43)</td>
</tr>
<tr>
<td>Paediatric</td>
<td>2</td>
<td>74</td>
<td>P=0.45, I²=0%</td>
<td>0.80 (0.44 to 1.43)</td>
<td>0.80 (0.44 to 1.43)</td>
</tr>
<tr>
<td>Interaction z test: P=0.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung protective ventilation</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mandated</td>
<td>3</td>
<td>267</td>
<td>P=0.07, I²=0%</td>
<td>0.67 (0.44 to 1.03)</td>
<td>0.84 (0.61 to 1.16)</td>
</tr>
<tr>
<td>Not mandated</td>
<td>3</td>
<td>98</td>
<td>P=0.28, I²=13%</td>
<td>0.84 (0.61 to 1.16)</td>
<td>0.84 (0.61 to 1.16)</td>
</tr>
<tr>
<td>Interaction z test: P=0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

Literature search

We identified 2995 citations from searches of electronic bibliographic databases and eight original citations from other sources. We retrieved 26 studies for detailed evaluation, of which eight trials met criteria for this review (fig 1). Details of excluded studies are in appendix 1 on bmj.com. Reviewers agreed on all studies for inclusion. Primary investigators provided additional clinical or physiological data or clarification of data or methods.

Study characteristics and quality of methods

The eight included trials enrolled a total of 431 patients (median 41, range 16-148) with acute lung injury and ARDS (table 1-3). Seven trials enrolled patients exclusively with ARDS (n=361), and 86% (n=52) of the patients in the eighth trial had ARDS. Two trials enrolled only children. Two trials are currently published only as abstracts. All trials studied high frequency oscillation as an initial ventilation strategy for acute lung injury or ARDS, as opposed to rescue treatment for refractory hypoxaemia. Trials enrolled patients within 48 hours of diagnosis of ARDS or shortly after initiation of mechanical ventilation (mean of less than two days or five days). All trials treated patients continuously with high frequency oscillation except for one that applied high frequency oscillation by protocol for 6-24 hours a day until predefined criteria for resolution of severe ARDS had been met (most patients were treated for at least four days). In two trials patients were treated for <24 hours. The median baseline PaO₂/FiO₂ ratio was 112 (range 80-122) in seven trials. All studies implemented high frequency oscillation according to a protocol and described conventional
mechanical ventilation (table 2, and appendix 2 on bmj.com). Five trials mandated low tidal volume ventilation (<8 ml/kg) in the control group, 50,52-55 and four trials mandated plateau pressure <35 cm H2O. 50,53-55

Six trials had high methodological quality and a low risk of bias. 50,55 The risk of bias was unclear in two studies. 48,49 All trials concealed allocation and analysed clinical outcomes for patients by assigned group 48,53-55 or provided enough information to perform analyses according to assigned group. 44 One trial was terminated early because of low recruitment. 46 Six trials reported no withdrawals after randomisation 49,50-52,55; in two trials, 1.4% (2/148) 44 and 17% (12/70) 44 of patients were withdrawn after randomisation. After contacting investigators, we obtained mortality data for withdrawn patients in one trial. 44 There was no loss to follow-up in seven studies. 48,50-54 One study provided mortality data from intensive care only, but not 30 day mortality, for 5% (3/61) of patients. 45 Five trials reported crossovers between groups (range 4-52% of all randomised patients), 44,49,51,52,54 which involved 0-19% of patients randomised to high frequency oscillation (7/37, 46 1/11,29, 46 0/6, 54 0/27, 25 and 4/75 44) and 7-65% of patients randomised to conventional ventilation (4/24, 49 19/29, 48 1/10, 54 2/27, 22 and 9/73 44).

Clinical outcomes

Table 4 summarises the clinical outcomes.

Mortality

In the primary analysis including six trials that treated patients with high frequency oscillation until resolution of ARDS 48,49,51,52,54,55 (n=363), the median hospital or 30 day mortality in the control group was 48% (range 33-67%). High frequency oscillation significantly reduced mortality at hospital discharge 52,54 or 30 days 48,49,51,55 (risk ratio 0.77, 95% confidence interval 0.61 to 0.98, P=0.03; fig 2). In one trial, 3/61 patients were alive at discharge from the intensive care unit and assumed to be alive at 30 days; censoring these patients does not alter the results of the meta-analysis (0.77, 0.61 to 0.98, P=0.04). Subgroup analyses (fig 3) did not show significant differences in treatment effect among four trials in adults 40,51,52,55 (n=291) compared with two trials in children 48,54 (n=74) (P=0.91 for interaction z test) or four trials (n=246) at low 51,52,54,55 compared with two trials (n=119) at high or unclear 48,49 risk of bias (P=0.15 for interaction z test). In a post hoc analysis (fig 3), there was no significant difference in treatment effect among three trials 48,49,51 (n=98) that mandated tidal volumes <8 ml/kg in the control group and three trials 48,49,51 (n=267) that allowed higher tidal volumes (z test for interaction, P=0.41, fig 3). Only one trial 53 (n=148) reported mortality at six months, with no significant effect of high frequency oscillation (0.79, 0.58 to 1.08, P=0.14). No trial reported on health related quality of life.

There was no evidence of publication bias. Visual inspection of a funnel plot showed no asymmetry, and neither Begg’s rank correlation test (P=0.45) nor Macaskill’s regression test (P=0.94) was significant.

Treatment failure and duration of mechanical ventilation

In five trials (n=337) high frequency oscillation reduced the risk of treatment failure compared with conventional mechanical ventilation (risk ratio 0.67, 0.46 to 0.99, P=0.04; fig 4). 48,49,51,52,54 Three trials (n=267) reported treatment failure according to predefined criteria (oxygenation failure, ventilation failure, hypotension, or barotrauma) that resulted in discontinuation of the assigned ventilation strategy. 48,49,51 Two trials (n=70) did not report this outcome, but we obtained data directly from the authors. 32,54 In one trial, one patient randomised to conventional ventilation with early treatment failure who crossed over to high frequency oscillation because of barotrauma was analysed as treatment failure in the conventional mechanical ventilation group. 54 If two patients randomised to conventional ventilation in another trial 32 who crossed over to high frequency oscillation for only three and six hours are not counted as treatment failures, the pooled result is no longer significant (0.69, 0.46 to 1.01, P=0.06). No trial reported blinding of outcome assessors or independent adjudication of treatment failure.

Neither the duration of mechanical ventilation (mean difference −0.8 days, −5.4 to 3.9 days, P=0.75; four trials, 48,51,52,54 n=276, see fig A5 in appendix 2 on bmj.com) nor ventilator-free days to day 28 (2.0 days, −0.7 to 4.7 days, P=0.15; one trial, 32 n=54) significantly differed between groups.

There was no evidence of heterogeneity (I²=0%) for any clinical outcome.

Physiological outcomes

Table 5 and figure 5 summarise the physiological outcomes. Further details are in appendix 2 on bmj.com. Figure 5 shows the results for PaO2/FiO2 ratio in days 1, 2, and 3. Day 1 measurements were obtained at 24 hours, except in two studies where they were obtained at 12 hours. 50,53 Analyses are by intention to treat except for one patient in one trial, 32 who crossed over from conventional ventilation to high frequency oscillation shortly after randomisation and was analysed as treated because we were unable to obtain sufficient data (after contacting the author) to permit an intention
to treat analysis. One trial combined tracheal gas insufflation and recruitment manoeuvres with high frequency oscillation; a randomised crossover trial showed that these co-interventions improve oxygenation. Results were similar when we excluded the data from this trial: 1.22 (1.05 to 1.40, P=0.008, I²=48%) on day 1, 1.05 (0.92 to 1.19, P=0.48, I²=6%) on day 2, and 1.09 (0.97 to 1.22, P=0.14, I²=0%) on day 3.

At 24, 48, and 72 hours, high frequency oscillation increased PaO₂/FiO₂ ratio by 16-24% relative to conventional mechanical ventilation and increased mean airway pressure by 22-33%. Effects on the oxygenation index and PaCO₂ did not significantly differ between high frequency oscillation and conventional ventilation. Heterogeneity was moderate for most analyses of physiological outcome (I²=21-78%), but extreme (I²≥90%) for the pooled analyses of PaCO₂.

### DISCUSSION

In patients with acute lung injury or ARDS, high frequency oscillation reduced hospital and 30 day mortality and decreased the risk of treatment failure. Although high frequency oscillation had no effect on the duration of mechanical ventilation, it improved oxygenation, as measured by the PaO₂/FiO₂ ratio, probably by increasing transpulmonary pressure and recruiting collapsed alveoli. There was no effect on oxygenation index because of the higher mean airway pressure during high frequency oscillation. Overall, high frequency oscillation had no effect on PaCO₂, though the effects in individual trials were markedly inconsistent. Similarly, high frequency oscillation was not associated with an increase in adverse events.

### Strengths and limitations

Our methods minimised bias by including a comprehensive literature search, abstracting data in triplicate, and using a predefined protocol outlining our hypotheses, methodological assessment of primary studies, and planned statistical analysis. We considered important clinical, physiological, and safety end points. Although blinding of patients, their families, and clinicians was not feasible, six of eight trials had high methodological quality and low risk of bias. Clinical outcomes were consistent across studies, including those that enrolled adults and children, strengthening the findings.
Table 5 | Physiological outcomes on days 1 to 3 after randomisation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of trials</th>
<th>No of patients</th>
<th>Treatment effect</th>
<th>Heterogeneity, I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1 (24 hours)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{PaO}_2/\text{FiO}_2)</td>
<td>7</td>
<td>233</td>
<td>1.24 (1.11 to 1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>7</td>
<td>331</td>
<td>1.33 (1.27 to 1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>6</td>
<td>294</td>
<td>1.11 (0.97 to 1.26)</td>
<td>0.12</td>
</tr>
<tr>
<td>(\text{PaCO}_2)</td>
<td>3</td>
<td>300</td>
<td>0.91 (0.78 to 1.07)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

| **Day 2 (48 hours)**  |              |                |                  |                       |
| \(\text{PaO}_2/\text{FiO}_2\) | 5            | 262            | 1.16 (0.97 to 1.37) | 0.10 | 62 |
| Mean airway pressure  | 5            | 262            | 1.26 (1.16 to 1.37) | <0.001 | 58 |
| Oxygenation index     | 5            | 259            | 1.07 (0.92 to 1.24) | 0.38    | 39 |
| \(\text{PaCO}_2\)     | 5            | 263            | 0.87 (0.72 to 1.06) | 0.16    | 95 |

| **Day 3 (72 hours)**  |              |                |                  |                       |
| \(\text{PaO}_2/\text{FiO}_2\) | 5            | 228            | 1.17 (1.02 to 1.35) | 0.02    | 44 |
| Mean airway pressure  | 5            | 236            | 1.22 (1.07 to 1.39) | 0.003   | 78 |
| Oxygenation index     | 5            | 228            | 1.07 (0.88 to 1.29) | 0.51    | 58 |
| \(\text{PaCO}_2\)     | 6            | 267            | 0.98 (0.84 to 1.14) | 0.78    | 90 |

\(\text{PaO}_2/\text{FiO}_2\)=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; \(\text{PaCO}_2\)=arterial partial pressure of carbon dioxide.

*Mean value in high frequency oscillation group divided by mean value in conventional ventilation group.

Random effects models used for all meta-analyses.

The mortality benefit of high frequency oscillation could be overestimated because the control group in three studies, including the largest trial, which had the highest weighting in the pooled analysis, was exposed to higher tidal volumes (>6-8 ml/kg predicted body weight) than currently recommended. Subgroup analysis, however, showed a similar benefit in trials that implemented lower tidal volumes in the control group. Alternatively, the higher rate of crossovers because of treatment failure in patients randomised to conventional ventilation might have reduced the measured effect of high frequency oscillation on mortality. In two studies that enrolled 30% of patients included in our review, more than 10% crossed over from their assigned mode of ventilation, highlighting an important methodological challenge in clinical trials of high frequency oscillation. Another opportunity to improve the success of future trials of high frequency oscillation would be to adopt consistent protocols for its optimal application. In our review, only one study routinely applied recruitment manoeuvres as part of the high frequency oscillation technique, and no trial attempted to maximise the frequency of oscillation to obtain the smallest possible tidal volume.

Though our primary analysis showed improved hospital or 30 day mortality, it was based on relatively few patients and outcome events and has wide confidence intervals. Similarly, for the meta-analysis of treatment failure, when the two patients randomised to conventional ventilation in one trial, who were only briefly crossed over to high frequency oscillation were not counted as treatment failures, the pooled result was no longer significant \((P=0.06)\). The specific events included in the definition of treatment failure varied across trials, none of which reported blinded outcome assessors or independent adjudication of treatment failure.

The decreased risk of mortality in patients who received high frequency oscillation is consistent with results of experimental studies in animals, showing that histological alveolar overdistension is reduced by high frequency oscillation compared with conventional mechanical ventilation, possibly because tidal volumes are smaller. Although improved oxygenation might not always be associated with improved clinical outcomes in ARDS, from a clinical perspective high frequency oscillation allows higher mean
The risk of death in patients with ARDS is high and seems stable over the past decade. In our review, the median mortality in the control group was 48%. As shown in a recent observational study of patients with H1N1 flu, many patients with severe ARDS required inhaled nitric oxide, prone positioning, high frequency oscillation, or extracorporeal membrane oxygenation, usually for refractory hypoxaemia. These treatments have different risk-benefit profiles. Inhaled nitric oxide is expensive, has not been shown to reduce mortality, and could cause harm. Extracorporeal membrane oxygenation might reduce mortality but is a specialised technique that is not widely available and requires systemic anticoagulation, which increases the risk of morbidity and mortality related to bleeding. Mechanical ventilation in the prone position reduces mortality in severely hypoxaemic patients and is inexpensive, but complications and interference with other aspects of patient care might limit its application. Our review suggests that high frequency oscillation is a safe and effective alternative to conventional ventilation in patients with ARDS, at least in centres proficient with its use.

### Future research

The limitations of current data will be addressed by two ongoing trials of high frequency oscillation compared with conventional ventilation (see appendix 1 on bmj.com). Each trial applies a lung protective approach to the control group, and collectively they will enrol more than 2000 patients. In the pilot phase of one of these trials, crossovers between randomly assigned ventilation strategies outside of protocol were infrequent. These trials will therefore compare high frequency oscillation with best current conventional ventilation and will provide more precise estimates of treatment effect.

### Conclusion

In summary, based on the available data, high frequency oscillation might reduce mortality in patients with ARDS compared with conventional ventilation and is unlikely to cause harm. It improves the PaO2/FiO2 ratio by increasing the mean airway pressure but not the oxygenation index. Clinicians who currently use or are considering high frequency oscillation to treat ARDS can be reassured by these results. Completion of ongoing multicentre randomised controlled trials will provide more definitive data on mortality and safety for this intervention.
involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors had: (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) the following non-financial interests relevant to the submitted work: MDM and NDF are primary investigators and JOF and NKJA are co-investigators for the ongoing Canadian Institutes of Health Research (CIHR) funded OSCILLATE study. CareFusion (formerly SensorMedics) is providing study oscillators to some of the hospitals involved in the OSCILLATE study for the duration of the study.

Ethical approval: Not required.

Data sharing: The protocol for the systematic review and dataset (RevMan 5.0 format) are available by request to the corresponding author.

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