

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. There were no significant differences in oxygenation index because mean airway pressure rose by 22-33% in patients receiving high frequency oscillation (P<0.01). In patients randomised to high frequency oscillation, mortality was significantly reduced (risk ratio 0.77, 95% confidence interval 0.61 to 0.98, P=0.03; six trials, 365 patients, 160 deaths), and treatment failure (refractory hypoxaemia, hypercapnoea, hypotension, or barotrauma) resulting in discontinuation of assigned therapy was less likely (0.67, 0.46 to 0.99, P=0.04; five trials, 337 patients, 73 events). Other risks were similar. There was substantial heterogeneity between trials for physiological (I²=21-95%) but not clinical (I²=0%) outcomes. Pooled results were based on few events for most clinical outcomes.

Conclusion High frequency oscillation might improve survival and is unlikely to cause harm. As ongoing large multicentre trials will not be completed for several years,

these data help clinicians who currently use or are considering this technique for patients with ARDS.

INTRODUCTION

Acute lung injury and acute respiratory distress syndrome (ARDS) are life threatening conditions characterised by acute lung inflammation causing pulmonary congestion, hypoxaemia, and decreased pulmonary compliance. Acute lung injury is common¹ and is associated with substantial mortality,^{1,2} morbidity,^{3,4} 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 distension, 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.^{1,2}

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.²⁸ Additional studies have subsequently become available. Furthermore, in the context of current^{29,30} and future pandemics, there is a pressing need for evidence on the effects of

Table 1 Characteristics of populations of patients and risk of bias⁴⁰ in trials included in systematic review

	No of patients	Mean age (years)	Setting	Days of ventilation before study	Details of lung injury	Overall risk of bias*
Arnold et al, ⁴⁸ 1994	70 (weight ≤35 kg)	2.8	5 US paediatric ICUs	4.5†	ARDS (86%) or pulmonary barotrauma requiring chest tube (14%)	Unclear (>10% (30/58) crossovers; outcome data for 12/70 patients not available after author contact)
Derdak et al, ⁵¹ 2002	148	49	ICUs in 13 US hospitals	1.9†	ARDS; PEEP >10 cm H ₂ O	Low
Shah et al, ⁵⁵ 2004‡	28	49	1 ICU in Cardiff	<5	ARDS	Low
Bollen et al, ⁴⁹ 2005	61	53	5 ICUs in 4 European cities	1.8†	ARDS	Unclear (>10% (11/61) crossovers; ICU but not 30 day mortality available for 3/61 patients after author contact; trial terminated early because of slow recruitment)
Papazian et al, ⁵³ 2005	26	51	1 ICU in Marseille, France	<1 (duration of ARDS <24 h)	ARDS; PaO ₂ /FiO ₂ ≤150, PEEP ≥5 cm H ₂ O	Low
Samransamruajkit et al, ⁵⁴ 2005	16 (weight ≤35 kg)	5	1 ICU in Bangkok, Thailand	<2 (duration of ARDS <48 h)	ARDS, PEEP >5 cm H ₂ O; FiO ₂ >0.6 for 12 h to keep SaO ₂ >92%; OI >15 for ≥4 h	Low
Demory et al, ⁵⁰ 2007	28	49	1 ICU in Marseille, France	<1 (duration of ARDS <24 h)	ARDS; PaO ₂ /FiO ₂ <150, PEEP ≥5 cm H ₂ O	Low
Mentzelopoulos et al, ⁵² 2007‡	54	57	1 ICU in Athens, Greece	3.5†	ARDS; PaO ₂ /FiO ₂ <150, PEEP 8 cm H ₂ O	Low

ICU=intensive care unit, ARDS=acute respiratory distress syndrome, PaCO₂=partial pressure of arterial carbon dioxide, PaO₂/FiO₂=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, PEEP=positive end expiratory pressure, SaO₂=oxygen saturation, OI=oxygation index.

*Studies classed as at low risk of bias if plausible bias was unlikely to seriously alter results, unclear risk of bias for plausible bias that raises some doubt about results, and high risk of bias for plausible bias that seriously weakens confidence in results. None of the included studies was blinded, and all studies reported adequate sequence generation, adequate concealment of allocation, and were free from selective outcome reporting.

†Mean.

‡Conference abstracts, with supplementary information provided by primary investigators.

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.³¹ 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 speciality; and searched for unpublished and ongoing trials

in clinicaltrials.gov and controlled-trials.com. There were no language restrictions.³²

Study eligibility

Two investigators (SS, MS), not blinded to study authors or results,³³ 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

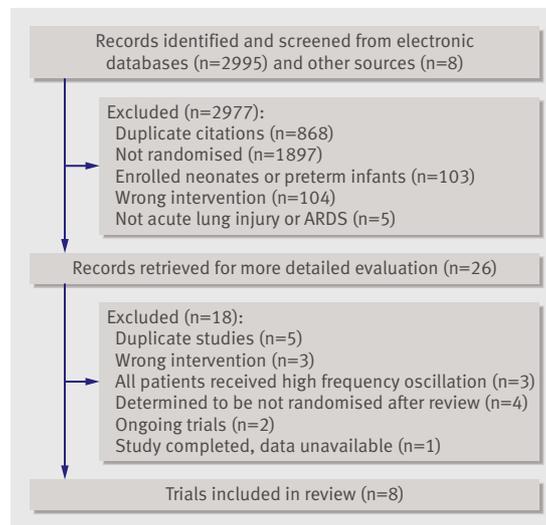
**Fig 1** Flow of studies included in review

Table 2 | Details of high frequency oscillation (HFO) and conventional mechanical ventilation (CMV) in trials included in systematic review

	High frequency oscillation					Conventional ventilation			
	Frequency (Hz)	Mean Paw (cm H ₂ O above CMV)	ΔP (cm H ₂ O) titration parameter or goal	Recruitment manoeuvre protocol	Criteria for transition to CMV	Mode	Tidal volume	Adjustment of PEEP (cm H ₂ O)	Recruitment manoeuvre protocol
Arnold et al, ⁴⁸ 1994	5-10	4-8	Achieve chest wall vibration or according to transcutaneous PCO ₂ sensor	No	Mean Paw 18 cm H ₂ O, tolerating suctioning	Pressure limited	NR	Clinician discretion	No
Derdak et al, ⁵¹ 2002	5	5	Achieve vibration from chest wall to mid-thigh	No	FiO ₂ <50%, mean Paw <24 cm H ₂ O	Pressure control	6-10 ml/kg actual body weight	10-18, by protocol	No
Shah et al, ⁵⁵ 2004‡	5	5	Achieve vibration from chest wall to mid-thigh	No	Until resolution of ARDS	NR	Mean 7-8 ml/kg ideal body weight*	NR	No
Bollen et al, ⁴⁹ 2005	5	5	According to PaCO ₂ ; achieve chest wall vibration	No	FiO ₂ <40%, PaO ₂ >60 mm Hg, tolerating suctioning	Pressure control	Mean 8-9 ml/kg ideal body weight†	NR	No
Papazian et al, ⁵³ 2005	5	5	Same PaCO ₂ as during CMV (max. 110)	At HFO initiation	After 12 hours of HFO	Volume assist control	6 ml/kg ideal body weight	2 above lower inflection point	No
Samransamruaj-kit et al, ⁵⁴ 2005	4-10	2-3	10 above peak inspiratory pressure during CMV	No	Mean Paw 18 cm H ₂ O, tolerating suctioning	Time cycled or pressure control	6-7 ml/kg ideal body weight	According to ARDS Network protocol ¹⁵	No
Demory et al, ⁵⁰ 2007	5	5 higher but ≤Pplat	Same PaCO ₂ as during CMV (max 110)	At HFO initiation	After 12 hours of HFO	Volume assist control	6-7 ml/kg predicted body weight	According to ARDS Network protocol ¹⁵	No
Mentzelopoulos et al, ⁵² 2007‡	4	3 above mean tracheal pressure measured distal to endotracheal tube	30 above baseline PaCO ₂ during CMV	Throughout HFO administration	After 6-24 h of HFO each day until PaO ₂ /FiO ₂ ≥150 for >12h on CMV	Volume assist control	6-7 ml/kg predicted body weight	According to ARDS Network protocol ¹⁵	Yes

ARDS=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 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 cross-over 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 (weaning, 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

	High frequency oscillation	Conventional mechanical ventilation	Sedation and paralysis applied equally to both groups	Protocols for ventilator weaning and extubation	Funding* (industry support)
Arnold et al, ⁴⁸ 1994	NR	NR	No	NR	Yes
Derdak et al, ⁵¹ 2002	Nitric oxide, 4/75; prone position, 2/75, high dose steroids, 1/75	Nitric oxide, 8/73; prone position, 3/73; high dose steroids, 4/73	No	No	Yes
Shah et al, ⁵⁵ 2004†	None	None	Yes	NR	No
Bollen et al, ⁴⁹ 2005	NR	NR	NR	No	Yes
Papazian et al, ⁵³ 2005	All patients ventilated in prone position	All patients ventilated in prone position	Yes	No	No
Samransamruajkit et al, ⁵⁴ 2005	Nitric oxide, 1/7	Nitric oxide, 0/9	Yes	No	No
Demory et al, ⁵⁰ 2007	Prone position for 12 h before HFO in supine position	Prone position for 12 h prior to CMV in supine position	Yes	No	No
Mentzelopoulos et al, ⁵² 2007‡	All patients received tracheal gas insufflation. Steroids for ARDS, 20/27	Steroids for ARDS, 21/27	No (27/27 HFO v 17/27 CMV patients paralysed)	Yes	No

NR=not reported, ARDS=acute respiratory distress syndrome.

*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 cross-over 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 (PaO₂) to inspired fraction of oxygen (FiO₂) (PaO₂/FiO₂ ratio); oxygenation index (OI, defined as 100×mean airway pressure/(PaO₂/FiO₂ ratio)); ventilation, measured by partial pressure of carbon dioxide (PaCO₂); and mean airway 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)⁴³ 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 I² measure^{44 45} and used published guidelines for low (I²=25-49%), moderate (I²=50-74%), and high (I²≥75%) heterogeneity.⁴⁵

To assess publication bias we examined funnel plots of treatment effect versus study precision and used Begg's rank correlation test⁴⁶ and a modified Macaskill's regression test.⁴⁷ Given the low statistical power

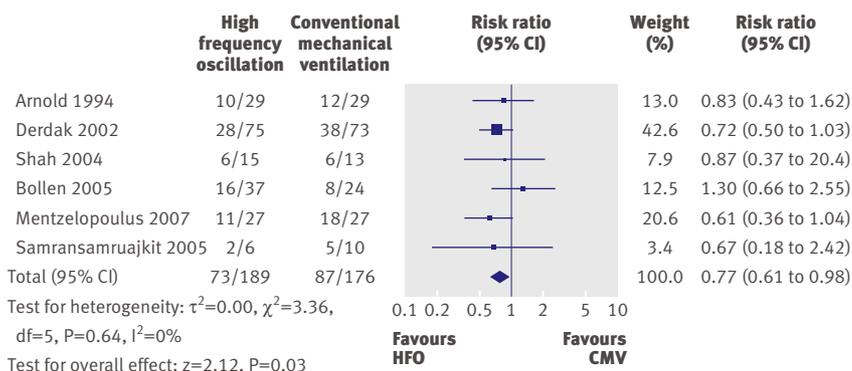


Fig 2 | Hospital or 30 day mortality in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

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

	No of trials	No of patients with events/ Total No of patients	Evidence assessment*	RR or WMD (95% CI), P value
Clinical outcomes				
Hospital (or 30 day) mortality	6	160/365	Moderate quality: randomised trials with some methodological limitations, no inconsistency ($I^2=0\%$), direct, some imprecision, no publication bias	0.77 (0.61 to 0.98), P=0.03
Treatment failure	5	73/337	Moderate quality: randomised trials with some methodological limitations, no inconsistency ($I^2=0\%$), direct, some imprecision	0.67 (0.46 to 0.99), P=0.04
Ventilator days	4	276†	Low quality: randomised trials with some methodological limitations, no inconsistency ($I^2=0\%$), direct, considerable imprecision	-0.8 days (-5.4 to 3.9), P=0.75
Ventilator free days to day 28	1	54†	Low quality: direct, considerable imprecision	2.0 days (-0.7 to 4.7), P=0.15
Adverse events				
Barotrauma	6	41/365	Low quality: randomised trials with some methodological limitations, no inconsistency ($I^2=0\%$), direct, considerable imprecision	0.68 (0.37 to 1.22), P=0.20
Hypotension	3	11/267	Low quality: randomised trials with some methodological limitations, no inconsistency ($I^2=0\%$), direct, considerable imprecision	1.54 (0.34 to 7.02), P=0.58
Endotracheal tube obstruction	4	7/246	Low quality: randomised trials with some methodological limitations, direct, considerable imprecision	1.30 (0.30 to 5.60), P=0.73

RR=relative risk; WMD=weighted mean difference.

*Quality of evidence for each outcome was assessed with GRADE⁴¹ recommendations. Principal determinant of quality for each outcome was degree of precision of estimate of treatment effect. Inconsistency refers to statistical heterogeneity, where measured, although I^2 might be underestimated when there are few trials. Sources of clinical heterogeneity included patient population, high frequency oscillation strategy, variable control group strategies, and variable definitions of treatment failure (see tables 1-3). Directness refers to extent to which patients, interventions, and outcome measures are similar to those of interest to systematic review. Imprecise results are those with wide confidence intervals that include both clinically significant benefit and harm. Publication bias was assessed for mortality only.

†Total No of patients.

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 on hospital or 30 day mortality in trials that mandated tidal volumes ≤ 8 ml/kg of predicted or ideal body weight in the control group compared with those that permitted higher tidal volumes. We assessed whether differences between subgroups were significant using a z test for interaction.

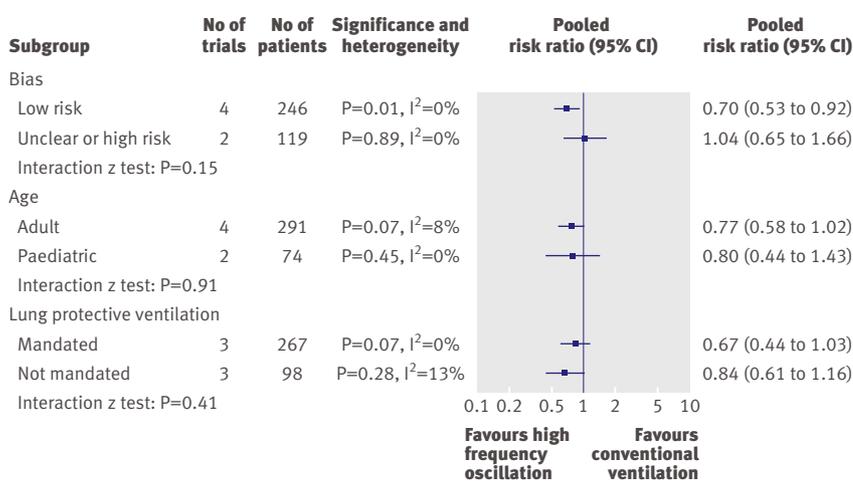


Fig 3 | Subgroup analyses based on age of patients, risk of bias, and use of lung protective ventilation in control groups

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 trials⁴⁸⁻⁵⁵ 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 clinical⁵⁰⁻⁵⁵ or physiological^{51,52,54,55} data or clarified data or methods.⁴⁸⁻⁵⁵

Study characteristics and quality of methods

The eight included trials⁴⁸⁻⁵⁵ enrolled a total of 431 patients (median 41, range 16-148) with acute lung injury and ARDS (tables 1-3). Seven trials⁴⁹⁻⁵⁵ enrolled patients exclusively with ARDS (n=361), and 86% (n=52) of the patients in the eighth trial had ARDS.⁴⁸ Two trials enrolled only children.^{48,54} Two trials are currently published only as abstracts.^{52,55} 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^{50,53,54} or shortly after initiation of mechanical ventilation (mean of less than two days^{49,51} or five days^{48,55}). 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).⁵² In two trials patients were treated for <24 hours.^{50,53} The median baseline $\text{PaO}_2/\text{FiO}_2$ ratio was 112 (range 80-122) in seven trials.^{48-51,53-55} All studies implemented high frequency oscillation according to a protocol and described conventional

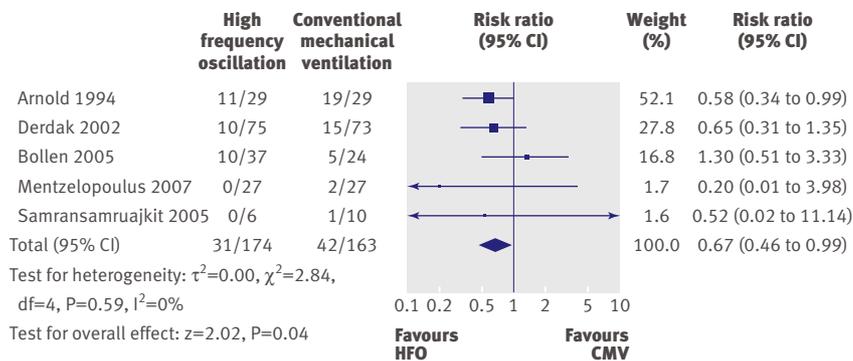


Fig 4 | Treatment failure in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

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 group⁴⁸⁻⁵³⁻⁵⁵ or provided enough information to perform analyses according to assigned group.⁵⁴ One trial was terminated early because of low recruitment.⁴⁹ Six trials reported no withdrawals after randomisation⁴⁹⁻⁵⁰⁻⁵²⁻⁵⁵; in two trials, 1.4% (2/148)⁵¹ and 17% (12/70)⁴⁸ of patients were withdrawn after randomisation. After contacting investigators, we obtained mortality data for withdrawn patients in one trial.⁵¹ There was no loss to follow-up in seven studies.⁴⁸⁻⁵⁰⁻⁵⁵ One study provided mortality data from intensive care only, but not 30 day mortality, for 5% (3/61) of patients.⁴⁹ Five trials reported crossovers between groups (range 4-52% of all randomised patients),⁴⁸⁻⁴⁹⁻⁵¹⁻⁵²⁻⁵⁴ which involved 0-19% of patients randomised to high frequency oscillation (7/37,⁴⁹ 11/29,⁴⁸ 0/6,⁵⁴ 0/27,⁵² and 4/75⁵¹) and 7-65% of patients randomised to conventional ventilation (4/24,⁴⁹ 19/29,⁴⁸ 1/10,⁵⁴ 2/27,⁵² and 9/73⁵¹).

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 ARDS⁴⁸⁻⁴⁹⁻⁵¹⁻⁵²⁻⁵⁴⁻⁵⁵ (n=365), the median hospital or 30 day mortality in the control group was 48% (range 33-67%). High frequency oscillation significantly reduced mortality at hospital discharge⁵²⁻⁵⁴ or 30 days⁴⁸⁻⁴⁹⁻⁵¹⁻⁵⁵ (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 adults⁴⁹⁻⁵¹⁻⁵²⁻⁵⁵ (n=291) compared with two trials in children⁴⁸⁻⁵⁴ (n=74) (P=0.91 for

interaction z test) or four trials (n=246) at low⁵¹⁻⁵²⁻⁵⁴⁻⁵⁵ compared with two trials (n=119) at high or unclear⁴⁸⁻⁴⁹ 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 trials⁵²⁻⁵⁴⁻⁵⁵ (n=98) that mandated tidal volumes ≤ 8 ml/kg in the control group and three trials⁴⁸⁻⁴⁹⁻⁵¹ (n=267) that allowed higher tidal volumes (z test for interaction, P=0.41, fig 3). Only one trial⁵¹ (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.⁵²⁻⁵⁴ 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 trial⁵² 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,⁵² 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,⁵⁴ 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

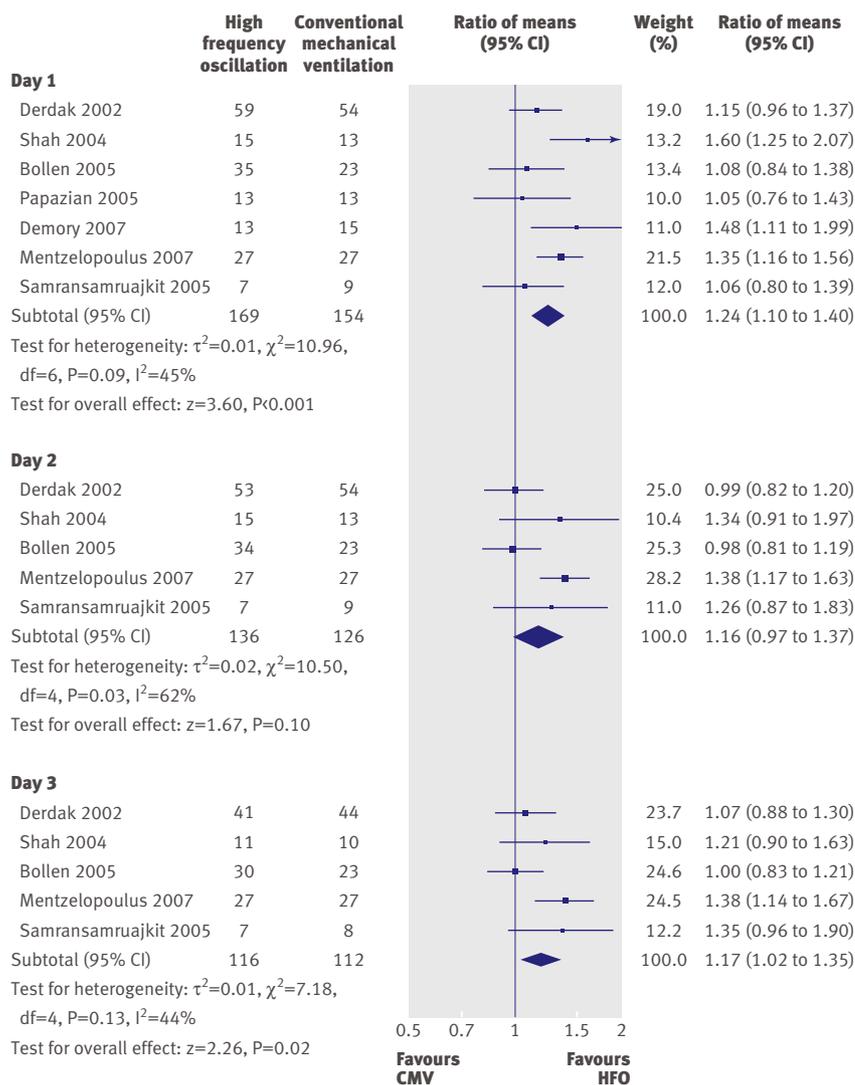


Fig 5 | PaO₂/FiO₂ ratio on days 1-3. Ratio of means is mean PaO₂/FiO₂ in high frequency oscillation group divided by mean PaO₂/FiO₂ in conventional mechanical ventilation group

to treat analysis. One trial combined tracheal gas insufflation and recruitment manoeuvres with high frequency oscillation⁵²; a randomised crossover trial showed that these co-interventions improve oxygenation.⁷³ Results were similar when we excluded the data from this trial⁵²: 1.22 (1.05 to 1.40, $P=0.008$, $I^2=48\%$) on day 1, 1.05 (0.92 to 1.19, $P=0.48$, $I^2=6\%$) on day 2, and 1.09 (0.97 to 1.22, $P=0.14$, $I^2=0\%$) 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 ($I^2=21-78\%$), but extreme ($I^2\geq 90\%$) for the pooled analyses of PaCO₂.

Adverse events

We found no significant differences (table 4) in the risk of barotrauma (six trials, $n=365$),^{48 49 51 52 54 55} hypotension (three trials, $n=267$),^{48 49 51} or endotracheal tube obstruction (four trials, $n=246$) (fig 6).^{51 52 54 55} Included studies varied in definitions of barotrauma: one study reported only pneumothorax,⁵⁵ three studies reported any pulmonary air leak,^{51 52 54} one study reported any pulmonary air leak that developed during protocol,⁴⁸ and one study reported severe air leak resulting in treatment failure.⁴⁹ Three studies reported intractable hypotension.^{48 49 51} Two other trials reported transient hypotension related to a procedure, associated with either bronchoscopy on day 1 (1/15 in high frequency oscillation group and 0/13 in conventional ventilation group⁵⁵), or recruitment manoeuvres on days 1-4 (11/27 and 8/27, respectively⁵²). Including these data minimally changed the pooled result (risk ratio 1.46, 0.77 to 2.76, $P=0.24$, $I^2=0\%$). Although four trials ($n=246$) reported on endotracheal tube obstruction,^{51 52 54 55} all events occurred in a single study, precluding a pooled analysis. There were no serious technical problems during high frequency oscillation in the three trials ($n=98$) that provided these data.^{52 54 55} One trial ($n=54$) reported minor technical problems, including over-efficiency of the humidifier that caused water accumulation in the circuit (number of instances not reported) and unintentional circuit leaks (five instances in 116 uninterrupted sessions lasting 6-48 hours).⁵²

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 compared with conventional mechanical ventilation. 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

Outcome	No of trials	No of patients	Treatment effect		Heterogeneity, I ² (%)
			Ratio of means* (95% CI)	P value	
Day 1 (24 hours)					
PaO ₂ /FiO ₂	7	323	1.24 (1.11 to 1.40)	<0.001	45
Mean airway pressure	7	331	1.33 (1.27 to 1.40)	<0.001	21
Oxygenation index	6	294	1.11 (0.97 to 1.26)	0.12	38
PaCO ₂	6	300	0.91 (0.78 to 1.07)	0.25	91
Day 2 (48 hours)					
PaO ₂ /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
PaCO ₂	5	263	0.87 (0.72 to 1.06)	0.16	95
Day 3 (72 hours)					
PaO ₂ /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
PaCO ₂	6	267	0.98 (0.84 to 1.14)	0.78	90

PaO₂/FiO₂=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PaCO₂=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,^{48,49,51} including the largest trial,⁵¹ 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.¹⁵ A 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,^{48,49} 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.⁵⁶ In our review, only one study routinely applied recruitment manoeuvres as part of the high frequency oscillation technique,⁵² and no trial attempted to maximise the frequency of oscillation to obtain the smallest possible tidal volume.⁵⁷

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 trial⁵² 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 blinding of outcome assessors or independent adjudication of treatment failure.^{48,49,51,52,54} The effects of high frequency

oscillation on clinical outcomes seemed to be consistent, but tests for heterogeneity are underpowered when there are few trials. Limited data precluded subgroup analyses based on degree of hypoxaemia and analyses of longer term mortality and health related quality of life, although the finding of a non-significant 21% relative risk reduction in six month mortality in one trial⁵¹ was consistent with the effect on hospital or 30 day mortality. We found moderate to high heterogeneity for physiological end points, limiting their interpretability. Because of limited data, we were unable to analyse duration of mechanical ventilation separately for survivors and non-survivors to address the possibility that differences in early mortality could drive overall differences in duration of mechanical ventilation. Thus, although our findings support high frequency oscillation as a promising treatment for acute lung injury and ARDS, the overall quality of the evidence is moderate for the most important clinical outcomes,⁴¹ and ongoing trials might affect these findings.

Findings in relation to other studies

Our findings differ from those of a Cochrane review in 2004, which did not find reduced mortality or treatment failure or improved PaO₂/FiO₂.²⁸ We included six additional trials of high frequency oscillation and unpublished data provided by primary investigators, which generated additional statistical power and more precise estimates of treatment effects.

The improvements we observed in PaO₂/FiO₂ are consistent with those in observational studies.²⁵⁻²⁷ Although high frequency oscillation increased PaO₂/FiO₂ compared with conventional ventilation, there was no difference in the oxygenation index (defined as 100 × mean airway pressure/(PaO₂/FiO₂ ratio)) because of higher mean airway pressure applied during high frequency oscillation. Although high mean airway pressure during conventional ventilation is commonly believed to harm the lungs,¹⁰ the importance of higher mean airway pressure during high frequency oscillation is unclear because of its incompletely characterised association with alveolar pressure, which is a more important determinant of lung injury in patients with ARDS. Direct comparisons of mean airway pressure and oxygenation index between high frequency oscillation and conventional ventilation might not be valid because mean airway pressures measured in the trachea during high frequency oscillation are 6-8 cm H₂O lower than values displayed on the ventilator, in contrast with conventional ventilation.⁵⁸

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,⁵⁹ possibly because tidal volumes are smaller.⁵⁷ Although improved oxygenation might not always be associated with improved clinical outcomes in ARDS,^{60,61} from a clinical perspective high frequency oscillation allows higher mean

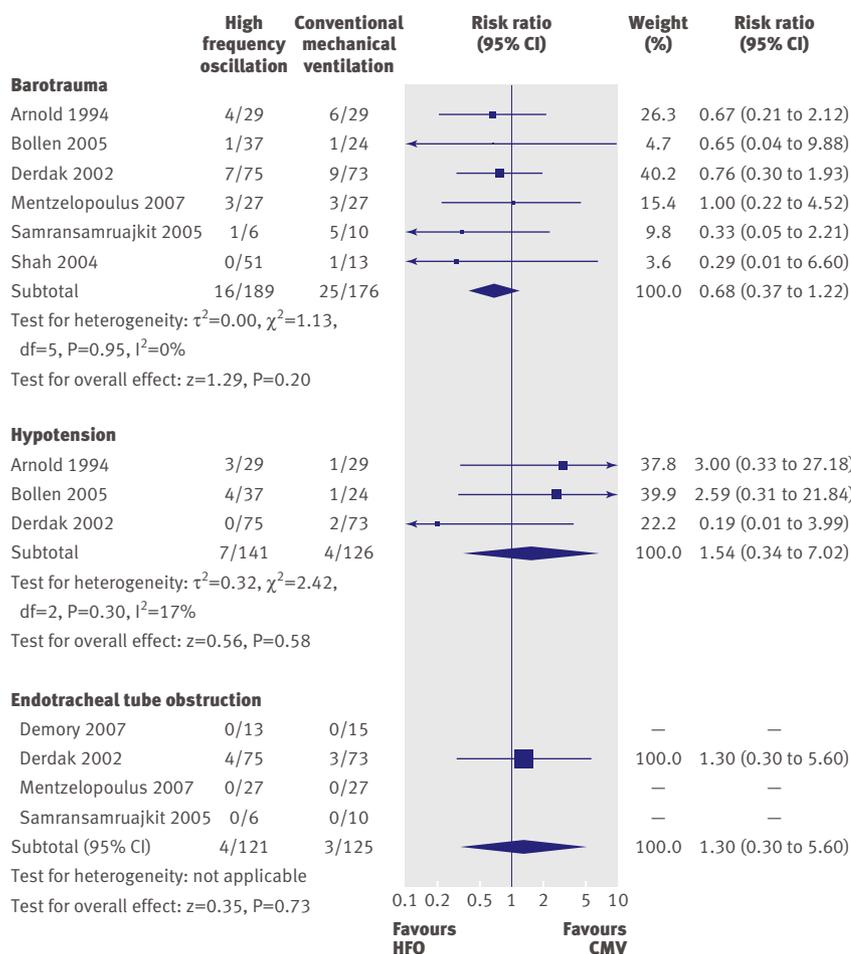


Fig 6 | Adverse events in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

airway pressures without increasing barotrauma and might therefore safely recruit collapsed lung.⁶² Increased lung recruitment and reduction of alveolar overdistension could reduce ventilator induced lung injury^{10,62} and provide a biological rationale for improved clinical outcomes.

Implications for practice

The risk of death in patients with ARDS is high¹² and seems stable over the past decade.² 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.²⁹ These treatments have different risk-benefit profiles.⁶³⁻⁶⁶ Inhaled nitric oxide is expensive, has not been shown to reduce mortality, and could cause harm.⁶⁵ Extracorporeal membrane oxygenation might reduce mortality but is a specialised technique that is not widely available⁶⁶ and requires systemic anticoagulation, which increases the risk of morbidity and mortality related to bleeding.⁶⁷ Mechanical ventilation in the prone position reduces mortality in severely hypoxaemic patients⁶⁴ and is inexpensive, but complications⁶⁸ and interference with other aspects of patient care might limit its application.^{69,70} 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.⁷¹ 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.

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Contributors: All authors contributed to study concept and design, revised the manuscript for important intellectual content, and approved the final version. SS conceived the study, acquired data, analysed and interpreted data, and drafted the manuscript. MS, JOF, and NKJA acquired, analysed, and interpreted data. MOM, NDF, and HW interpreted data. NKJA and JOF contributed equally to this study. SS, JOF, and NKJA are guarantors.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Some centres routinely use high frequency oscillation to support oxygenation in adults and children with acute respiratory distress syndrome (ARDS), although there is no clear evidence that it reduces mortality

An earlier systematic review found only two randomised trials and could not draw definitive conclusions regarding efficacy

WHAT THIS STUDY ADDS

In an updated review of eight randomised controlled trials, pooled results suggest that high frequency oscillation improves oxygenation and reduces the risk of treatment failure (refractory hypoxaemia, hypercapnoea, hypotension, or barotrauma) as well as hospital or 30 day mortality compared with conventional mechanical ventilation in patients with ARDS

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: MOM 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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