High-frequency Ventilation Does Not Provide Mortality Benefit in Comparison with Conventional Lung-protective Ventilation in Acute Respiratory Distress Syndrome

A Meta-analysis of the Randomized Controlled Trials

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ABSTRACT

Background: Despite implementation of lung-protective ventilation strategy, acute respiratory distress syndrome is associated with significant mortality, which necessitates the evaluation of ventilatory modes other than conventional lung-protective strategy. This meta-analysis of the randomized controlled trials has been undertaken to know whether high-frequency oscillatory ventilation (HFOV) provides any mortality benefit over conventional ventilation in adult patients with acute respiratory distress syndrome.

Methods: Published randomized controlled trials comparing HFOV with conventional lung-protective ventilation in adult patients with acute respiratory distress syndrome were included in this meta-analysis.

Results: A total 1,759 patient data from seven randomized controlled trials have been analyzed here. Primary outcome of the review is in-hospital/30-day mortality and secondary outcomes are duration of intensive care unit stay, duration of mechanical ventilation, requirement of additional treatment, and complications associated with the interventions. HFOV does not offer any in-hospital/30-day mortality benefit (386 of 886 in HFOV *vs.* 368 of 873 in conventional ventilation; risk ratio, 0.96; 95% CI, 0.77 to 1.19; $P = 0.70$) over conventional ventilation. It may also prolong the duration of mechanical ventilation (mean difference, 1.18 days; 95% CI, 0.00 to 2.35 days; $P = 0.05$). Duration of intensive care unit stay (mean difference, 1.24 days; 95% CI, –0.08 to 2.56 days; $P = 0.06$) and requirement of neuromuscular blocker is similar between two treatment arm. Incidence of refractory hypoxemia is significantly less (risk ratio, 0.60; 95% CI, 0.39 to 0.93; $P = 0.02$) with the use of HFOV. HFOV is not associated with increased incidence of barotrauma and refractory hypotension.

Conclusion: HFOV should not be used routinely in all adult patients with acute respiratory distress syndrome as primary ventilation strategy in place of conventional lung-protective ventilation. (**ANESTHESIOLOGY** 2015; 122:841-51)

A CUTE respiratory distress syndrome (ARDS) is a potentially life-threatening hypoxic respiratory failure, characterized by arterial hypoxemia (Pa_{O_2}/F_{IO_2} <200), pulmonary congestion, and decreased respiratory compliance. ARDS is associated with substantial in-hospital mortality and long-term complications.[1] Berlin definition[2] classified ARDS in three categories based on degree of hypoxemia: mild (200 mmHg < Pa_{O_2}/F_{IO_2} ≤ 300 mmHg), moderate (100 mmHg < Pa_{O_2}/F_{IO_2} ≤ 200 mmHg), and severe (Pa_{O_2}/F_{IO_2} ≤ 100 mmHg).

Mechanical ventilation is usually required during management of ARDS to combat arterial hypoxemia[3]; however, mechanical ventilation itself incites a new inflammatory process because of stretching of the alveoli.[4] Ventilation with a small tidal volume (6 ml/kg of ideal body weight) has become the standard of care in contemporary clinical practice for fear

> **What We Already Know about This Topic**
> - There have been conflicting results from clinical studies utilizing high-frequency oscillatory ventilation for patients with acute respiratory distress syndrome
>
> **What This Article Tells Us That Is New**
> - A meta-analysis of 1,759 patients from seven randomized controlled trials documents that the use of high-frequency oscillatory ventilation does not offer a mortality benefit and appears to prolong the duration of mechanical ventilation

of more lung injury because of overstretching.[5] A Cochrane review[6] has found that low-tidal-volume ventilation is associated with significantly less in-hospital and 28-day mortality. Positive end-expiratory pressure may also be a component of lung-protective ventilation to minimize atelectotrauma.[7] However, despite "lung-protective ventilatory strategy,"

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mortality from ARDS remains high[8] and may necessitate requirement of other ventilation strategies.

High-frequency oscillatory ventilation (HFOV) is an alternate ventilation technique in which very small tidal volumes (1 to 4 ml/kg of ideal body weight) are delivered at very high (3 to 15 Hz) frequencies using an oscillatory pump while mean airway pressure is held constant.[9] Mean airway pressure is determined by the bias flow and the resistance valve and gas exchange occurs because of gas mixing as opposed to bulk flow in conventional ventilation.

High-frequency oscillatory ventilation has been used in several observational studies as rescue therapy where conventional ventilation failed to maintain adequate oxygenation or it could not be safely applied.[10] Fort et al.[11] in a pilot study found that HFOV is a safe and effective ventilation strategy in adult patients with ARDS. A retrospective analysis in 2004 opined that high-frequency ventilation might have a beneficial effect on oxygenation in patients with ARDS.[12] Mehta et al.[13] in a prospective observational study found similar findings and they concluded that early use of HFOV may be advantageous. A previous meta-analysis[14] in 2010 concluded that HFOV may improve survival and does not cause any harm in patients with ARDS. Another previous Cochrane review[15] found that HFOV reduced in-hospital mortality and 30-day mortality in patients with ARDS and decreased the risk of treatment failure when compared with conventional mechanical ventilation. Since the publication of that review, another three well-designed large randomized controlled trials (RCT)[16–18] have been published. Among the latest three RCTs, one trial reported higher survival to hospital discharge with use of HFOV and tracheal gas insufflation. The other two RCTs did not find any benefit of HFOV in reducing in-hospital mortality in patients with ARDS. Therefore, we conducted a new meta-analysis and systemic review to determine whether HFOV is equally or more beneficial than conventional lung-protective ventilation strategy in patients with ARDS.

Materials and Methods

Protocol and Registration
A protocol for this meta-analysis has not been registered.

Eligibility Criteria
Published, prospective, RCTs comparing the safety and efficacy of HFOV with conventional ventilations in adult patients with ARDS and reporting either in-hospital/30-day mortality or length of intensive care unit (ICU) stay were included in this review. We did not consider trials on children, in contrast to the previous meta-analysis and Cochrane review. Trials where a secondary respiratory adjunct therapy was used along with high-frequency oscillation, such as tracheal gas insufflation or recruitment maneuvers, were also included in this meta-analysis. We neither sought for unpublished trials nor contacted the authors for unpublished data. However, we used the data from previous meta-analyses and reviews. We did not restrict our search to studies published in any particular language.

Information Source and Search Method
The three authors (S.M., S.B., and P.K.) independently searched PubMed, PubMed Central, Scopus, and Central Register of Clinical Trials of the Cochrane Collaboration for eligible controlled trials using the following search words: "high frequency oscillation," "high frequency ventilation," "conventional ventilation," "ARDS," and "ALI" from 1985 to June 2013. We also manually searched reference lists from included studies. The detail of search strategy in PubMed is mentioned in the appendix. Studies on hypoxemic respiratory failure other than ARDS were not considered for inclusion in this review.

Study Selection
Two authors (S.M. and S.B.) independently read the abstract of the potentially eligible trials. Both of them selected eligible trials as per inclusion criteria. When a difference in opinion was encountered, the opinion of the third author (D.K.B.) was considered to be final.

Data Collection
We collected the required data from the full text of the trials. Initially all data were tabulated in Microsoft Excel spreadsheets (Microsoft Corp., Redmond, WA). S.M. and S.B. initially extracted data from the eligible trials and those data were cross-checked independently by P.K. and D.K.B. Statistical analyses were performed by S.M.

Data Items
The following data were collected from each study: name of the first author, year of publication, total number of patients studied, patient population, time of institution of HFOV, in-hospital/30-day/28-day mortality (primary outcome), duration of mechanical ventilation, length of ICU stay, treatment failure leading to crossover to the other arm or discontinuation of the study protocol, and physiological variables (mean airway pressure, oxygenation index [OI], Pa_{O_2}/F_{IO_2} ratio [P/F ratio], Pa_{CO_2}, and arterial pH) at days 1, 2, 3, 5, and 7 (secondary outcomes). Requirement of neuromuscular blockade drugs and vasopressors/inotropes was also tabulated. We accepted the definition of the disease (acute lung injury/ARDS) and definitions of treatment failure, which could include severe oxygenation failure, ventilation failure, hypotension, or barotraumas (pneumothorax, pneumomediastinum, and subcutaneous emphysema) as described by the authors.

Risk of Bias Assessment
The quality of eligible trials was assessed using the tool of "risk of biases" according to Review Manager, version 5.2.3 software (Review Manager; The Nordic Cochrane Centre, Copenhagen, Denmark).[19] Random sequence generation,

allocation concealment, blinding, incomplete data, and selective reporting were assessed by one author (D.K.B.) based on the methodology of the trials. Each was graded "yes," "no," or "unclear" that reflected a high risk of bias, low risk of bias, and uncertain bias, respectively. All the studies included here are randomized, but for obvious technical reasons, all are prone to performance and detection bias. Risk of biases in the individual studies has been provided in figure 1. Publication bias was assessed by visual inspection of funnel plot and also by Begg rank correlation test[20] and also by Rosenthal classic failsafe N.

Statistical Analysis

Statistical analyses of the pooled data were done by Review Manager, version 5.2.3 software, and publication bias was tested by metabias command in Stata 12.0 for Windows (StataCorp LP, College Station, TX). Primary outcome of the meta-analysis was in-hospital mortality/28-day/30-day mortality and length of ICU stay. The secondary outcomes were long-term/6-month mortality, duration of mechanical ventilation, treatment failure leading to crossover to the other arm or discontinuation of the study protocol, and any other complications (hypotension, pneumothorax, hypercarbia, and many more). For binary outcome (in-hospital mortality or 30-day mortality, length of ICU stay, and treatment failure), we calculated the following: (1) the risk ratio for each trial, (2) the pooled risk ratio using the Mantel–Haenszel (M-H) method, (3) the number needed to treat, that is, the number of patients who must be treated for one patient to benefit from the intervention where a statistical significance was found.

For continuous variables (duration in mechanical ventilation, duration of ICU stay, and many more), mean and SD values were extracted for both groups, a mean difference (MD) was computed at the study level, and a weighted mean difference was computed to pool the results across all studies. If the values were reported as median and an interquartile range or total range of values in any RCT, the mean value was estimated using the median and the low and high end of the range for samples smaller than 25; for samples greater than 25, the median itself was used. The SD was estimated from the median and the low and high end of the range for samples smaller than 15, as range divided by 4 for samples from 15 to 70, and as range divided by 6 for samples more than 70. If only an interquartile range was available, SD was estimated as interquartile range divided by 1.35.[21]

All statistical variables were calculated with 95% CI. The Q-test was used to analyze heterogeneity of trials. When I^2 greater than 50%, it was considered as heterogeneous and the random model was performed; otherwise fixed model was used. Wherever a fixed model was used, we rechecked it with a random model also. Publishing bias was tested by funnel plot.

Results

Literature Search

Electronic database searches revealed 1,078 unique articles, of which, after exclusion of irrelevant articles from title and abstract, a total of 25 studies were thoroughly screened by two independent authors (S.M. and S.B.). Finally, a total of seven prospective RCTs were considered to be included in this meta-analysis, where a comparison of in-hospital/30-day mortality has been made between high-frequency ventilation and conventional ventilation in adult patients with ARDS. Study selection protocol as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines has been depicted in figure 2. However, Hurst et al.[22] used high-frequency percussive ventilation, which is different from other high-frequency ventilatory modes and hence was excluded from the final analysis. A total of 1,759 patients have been included in this analysis.

Characteristics of the Included Studies

Seven prospective clinical studies[16–18,23–26] published between 2002 and 2013 have been included in this review.

Fig. 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study (green = no risk of bias; yellow = unclear risk of bias; red = possible risk of bias).
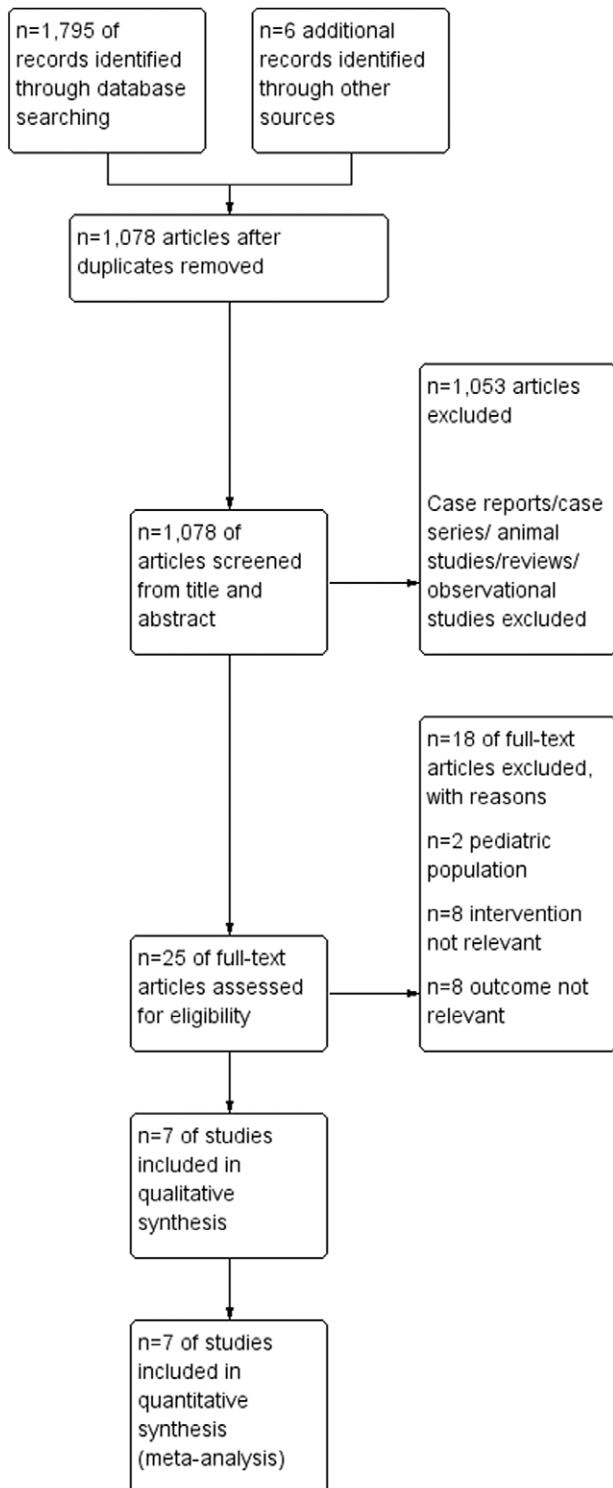
Fig. 2. Study selection flow diagram.

All trials studied high-frequency ventilation as an initial ventilation strategy for acute lung injury or ARDS, but not for rescue treatment for refractory hypoxemia. All trials used a lung-protective ventilation strategy, by targeting a tidal volume of 6 ml/kg or a plateau pressure of 30 to 35 cm H_2O or both and explicitly declared HFOV protocol for their study

populations. Details of ventilation strategy of the included trials have been depicted in table 1.

Demory et al.[26] recruited patients within 48 h of diagnosis of ARDS; Mentzelopoulus et al.[16] recruited patients within 72 h of diagnosis of ARDS; Derdak et al.,[23] Bollen et al.,[24] and Young et al.[18] initiated HFOV within a mean of 2 days of initiation of mechanical ventilation. Ferguson et al. recruited patients who had pulmonary symptoms for less than 7 days. In all trials, patients were treated by HFOV until a clinical set point was reached or resolution of ARDS occurred. Patient characteristics in the individual studies have been provided in table 2.

Characteristics of the Excluded Studies

We excluded clinical trials that recruited pediatric patients.[27,28] Because high-frequency ventilation is found to be most effective in neonates, age may influence the clinical outcome after HFOV use.

Clinical Outcome

Mortality. Pooled analysis from seven RCTs did not find any benefit in in-hospital/30-day mortality with high-frequency ventilation (risk ratio, 0.96; 95% CI, 0.77 to 1.19; M-H random; $P = 0.70$; fig. 3). A sensitivity analysis was also performed by excluding two large included studies[17,18] one by one, but the result of in-hospital mortality was not changed. However, after simultaneous exclusion of the above-mentioned studies, we found that HFOV provides significant mortality benefit over conventional ventilation (risk ratio, 0.81; 95% CI, 0.88 to 0.99; M-H fixed; $P = 0.04$). A random model analysis also found similar results (risk ratio, 0.81; 95% CI, 0.88 to 0.98; M-H fixed; $P = 0.03$). Mentzelopoulus et al.[25] Mentzelopoulus et al.,[16] and Ferguson et al.[17] determined mortality at discharge from hospital. Derdak et al.,[23] Bollen et al.,[24] and Young et al.[18] determined 30-day mortality. Demory et al.[26] used high-frequency ventilation for a 12-h period only, and Mentzelopoulus et al.[16] used high-frequency strategy intermittently; hence, we did an pooled analysis excluding these studies and found similar results (risk ratio, 0.97; 95% CI, 0.75 to 1.27; $P = 0.84$; M-H random).

A mandatory use of lung-protective ventilation may improve outcome in control group and so we did a subgroup analysis where a mandatory "lung-protective strategy" was used and where lung-protective strategy was suggested only. However, we did not find any superiority of HFOV in either subgroup over conventional ventilation. Details of this subgroup analysis have been provided in figure 4.

No evidence of publication bias has been found in funnel plot, Begg rank correlation test (Kendall tau = −0.06667; $P = 0.85$), and classic failsafe N (z value, −0.41412; $P = 0.67$, number of studies required to bring P value greater than alpha = 0).

Derdak et al.[23] reported 6-month mortality and Mentzelopoulus et al.[16] reported 150-day mortality, and the

Table 1. Ventilation Strategy in Included Trials

Author(s)	High-frequency Strategy	Conventional Ventilation Strategy
Derdak et al. 2002[23]	3100B high-frequency oscillatory ventilator. Initial settings: F_{IO_2} of 0.80–1.0, frequency of 5 Hz, mPaw of CV +5, pressure amplitude of oscillation set for "vibration down to level of mid-thigh," bias flow of 40 l/min	Vt of 6–10 ml/kg actual body weight, RR adjusted for pH >7.15, PEEP of 10 (adjustable up to 14), Ti 33%
	Back to CV when F_{IO_2} was 0.50 or less and mPaw was weaned to 24 cm H_2O or less with an Sao_2 of ≥88%	
Bollen et al. 2005[24]	3100B high-frequency oscillatory ventilator. Frequency of 5 Hz with Ti of 33%, mPaw of CV +5 cm H_2O, pressure amplitude of oscillation set according to $Paco_2$ and to achieve chest wall vibration.	Time cycled pressure control ventilation with a Vt of 8–9 ml/kg IBW and maximum PIP of 40 cm H_2O
Demory et al. 2007[26]	3100B high-frequency oscillatory ventilator. Initial settings were F_{IO_2} of 1.0, frequency of 5 Hz with Ti of 33%, mPaw of CV +5 cm H_2O (≤plateau pressure), pressure amplitude of oscillation = $Paco_2$ during conventional mechanical ventilation (maximum 110) for 24 h	Volume-assist control with Vt of 6–7 ml/kg predicted body weight and PEEP according to ARDSNet protocol
	All patients received conventional mechanical ventilation in the prone position for 12 h before HFO or conventional mechanical ventilation in the supine position	
Mentzelopoulos et al. 2007[25]	3100B high-frequency oscillatory ventilator. Frequency of 4 Hz, mPaw of 3 above mean tracheal pressure measured distal to the endotracheal tube, pressure amplitude of oscillation set 30 above baseline $Paco_2$ during CV	Volume-assist control with a Vt of 6–7 ml/kg of predicted body weight and Vt and PEEP adjusted according to ARDSNet protocol
	Patients received 6–24 h of HFO each day until Pao_2/F_{IO_2} ≥150 for >12 h on CV. All of them received tracheal gas insufflation with HFO	
Mentzelopoulos et al. 2012[16]	3100B high-frequency ventilator and a goal of each HFO-TGI to increase Pao_2/F_{IO_2} to 150 mmHg by using a high initial Paw (recruitment period) and then maintain the oxygenation benefit during a gradual Paw reduction to 6 cm H_2O below its initial value (stabilization period) and during weaning from TGI and HFO (weaning period)	Volume-assist control with Vt 6 ml/kg, RR 16–20/min, I:E = 1:2, PEEP and F_{IO_2} according to a predefined protocol
	HFO-TGI group received recruitment sessions of HFO-TGI with RMs according to prespecified oxygenation criteria. HFO-TGI sessions were interspersed with lung-protective CMV without RMs. The CMV group received lung-protective CMV and RMs for days 1–4 postrandomization	
Ferguson et al. 2013[17]	HFOV started with a mean airway pressure of 30 cm H_2O, adjusting the pressure thereafter according to the protocol, targeting a Pao_2 of 55–80 mmHg. HFOV tidal volumes were minimized by using the highest possible frequency that would maintain arterial pH >7.25	Target Vt of 6 ml/kg with plateau airway pressure ≤35 cm H_2O and high levels of PEEP (A PEEP–F_{IO_2} table was used)
	After 24 h of HFOV, CV was resumed if the mean airway pressure ≤24 cm H_2O for 12 h. Transition was mandatory when airway pressures reached 20 cm H_2O. Thereafter, mechanical ventilation followed the control protocol. During the next 48 h, if F_{IO_2} >0.4 or a PEEP >14 cm H_2O was required for >1 h to achieve oxygenation targets, HFOV was resumed	
Young et al. 2013[18]	Novalung R100 ventilator was used. Initial settings: frequency of 10 Hz, mPaw 5 cm H_2O above plateau airway pressure at enrollment, bias flow rate 20 l/min, a cycle volume of 100 ml, and F_{IO_2} 1.0	Conventional ventilation group was treated according to local protocol. Pressure-controlled ventilation at 6–8 ml/kg of IBW and ARDSNet protocol was encouraged
	$Paco_2$ was controlled to achieve arterial pH >7.25 by increasing cycle volume to the maximum at each frequency. If this was insufficient, the frequency was reduced by 1 Hz	

CMV = conventional mechanical ventilation; CV = conventional ventilation; F_{IO_2} = fraction of inspired oxygen; HFO = high-frequency oscillation; HFOV = high-frequency oscillatory ventilation; IBW = ideal body weight; I:E = inspiratory:expiratory time; mPaw = mean airway pressure; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; RM = recruitment maneuver; RR = respiratory rate; Sao_2 = arterial oxygen saturation; TGI = tracheal gas insufflations; Ti = inspiratory time; Vt = tidal volume.

Table 2. Patient Characteristics and Time of Randomization

Author(s)	Mode of Ventilation	Number of Patients (n)	Mean Age (Mean ± SD)	Ventilator Time before Randomization
Bollen et al.[24]	HFOV	37	81.0 ± 20.5	2.1 ± 2.6 days
	CV	24	81.7 ± 12.5	1.5 ± 1.8 days
Demory et al.[26]	CVpr-HFOVsup	13	45 ± 14	6 h
	CVpr-CVsup	15	52 ± 13	6 h
Derdak et al.[23]	HFOV	75	48 ± 17	2.7 ± 2.7 days
	CV	73	51 ± 18	4.4 ± 7.8 days
Ferguson et al.[17]	HFOV	275	55 ± 16	2.5 ± 3.3 days
	CV	273	54 ± 16	1.9 ± 2.3 days
Mentzelopoulos et al. 2007[25]	HFOV/HFOV + TGI/CV	14	18–75 yr	<72 h
Mentzelopoulos et al. 2012[16]	HFOV-TGI	61	50.7 ± 17.7	3.0 (1.0–5.5)
	CV	64	52.9 ± 17.1	2.0 (1.0–5.0)
Young et al.[18]	HFOV	398	54.9 ± 18.8	2.2 ± 2.3
	CV	397	55.9 ± 16.2	2.1 ± 2.1

CV = conventional ventilation; HFOV = high-frequency oscillatory ventilation; pr = prone; sup = supine; TGI = tracheal gas insufflations.
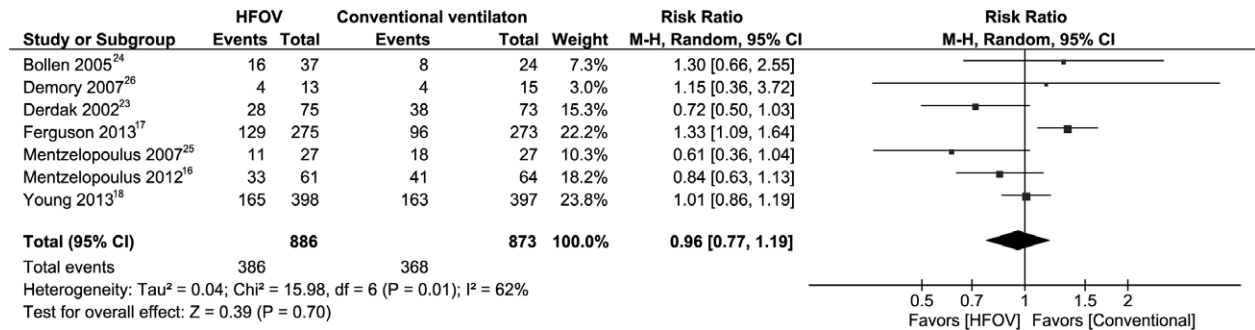

Fig. 3. Forest plot showing risk ratio of in-hospital mortality at individual study level and at pooled analysis level. HFOV = high-frequency oscillatory ventilation; M-H random = Mantel–Haenszel random model.

use of HFOV was associated with significantly less long-term mortality (risk ratio, 0.69; 95% CI, 0.55 to 0.88; P = 0.003; M-H fixed; n = 273). A random-effect analysis also found a benefit of using HFOV in long-term mortality (risk ratio, 0.70; 95% CI, 0.52 to 0.93; P = 0.01; M-H random).

Duration of ICU Stay. The three most recent trials[16–18] reported duration of ICU stay in either group of patients. Pooled analysis showed no statistically significant (MD, 1.24 days; 95% CI, –0.08 to 2.56 days; inverse variance fixed; P = 0.06; n = 1468; fig. 5) prolongation of duration of ICU stay in patients treated with HFOV. A random-effect analysis also found a similar result (MD, 1.24 days; 95% CI, –0.08 to 2.56 days; inverse variance random; P = 0.06). However, none of the studies reported criteria for discharge from the ICU and two of the included studies[17,19] are multicentric, and hence probability of biases remains.

Duration of Mechanical Ventilation. Six trials[16–18,23–25] reported duration of mechanical ventilation. A pooled analysis of 1,506 patients reported at least similar or prolonged duration of mechanical ventilation with HFOV (MD, 1.18 days; 95% CI, 0.00 to 2.35 days; P = 0.05;

inverse variance fixed; fig. 6). A random-effect model also found no different result from that of fixed-effect model (MD, 1.18 days; 95% CI, 0.00 to 2.35 days; P = 0.05; inverse variance random). All the trials included here used a predetermined specific weaning criterion for discontinuation of mechanical ventilation.

Requirements of Additional Treatment

Neuromuscular Blocker Use. A pooled analysis of data from three trials[16–18] (n = 1435) showed use of muscle relaxant was similar between patients treated with HFOV and conventional ventilation (risk ratio, 1.20; 95% CI, 1.00 to 1.44; P = 0.06; M-H random).

Inotrope/Vasopressor Use. Ferguson *et al.*[17] and Young *et al.*[18] reported number of days of use of inotropes/vasopressors. A pooled analysis revealed that there is no significant difference in days of inotrope/vasopressor use (MD, 1.04 days; 95% CI, –0.82 to 2.90 days; P = 0.27; M-H random).

Physiological Variables. Different trials reported various physiological variables (*e.g.*, mean airway pressure, peak airway pressure, plateau pressure, Pao_2, P/F ratio, OI, $Paco_2$, arterial pH, and other hemodynamic variables) at different time points.
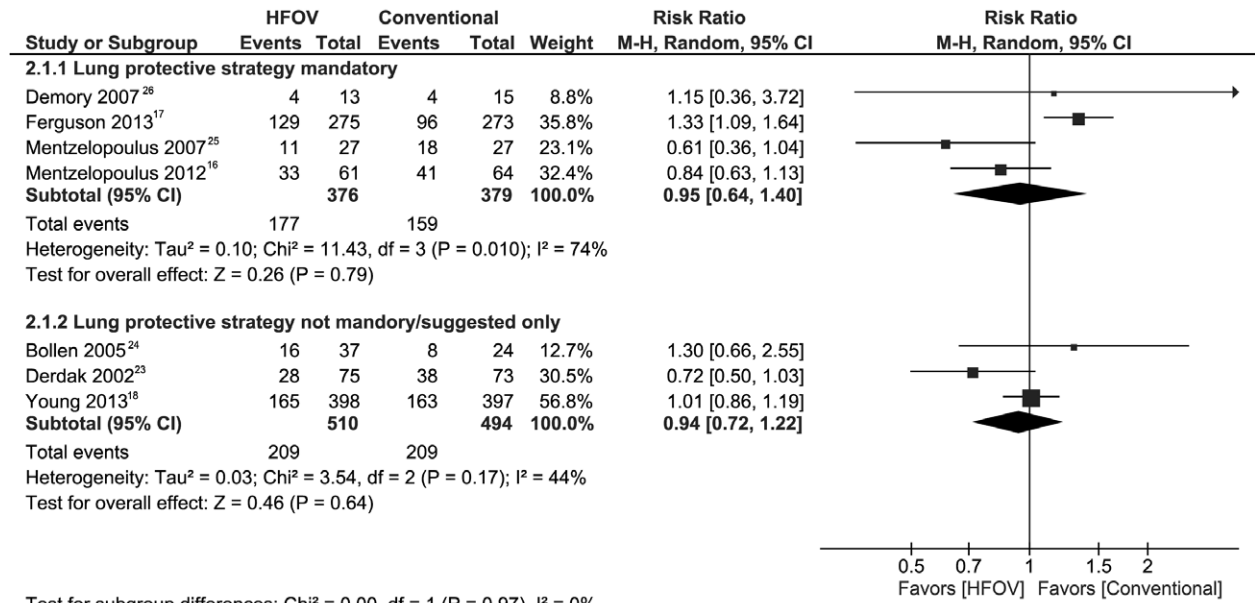
Fig. 4. Forest plot of subgroup analysis of in-hospital mortality/30-day mortality: Lung-protective strategy mandatory *versus* lung-protective strategy not mandatory/suggested. HFOV = high-frequency oscillatory ventilation; M-H random = Mantel–Haenszel random model.
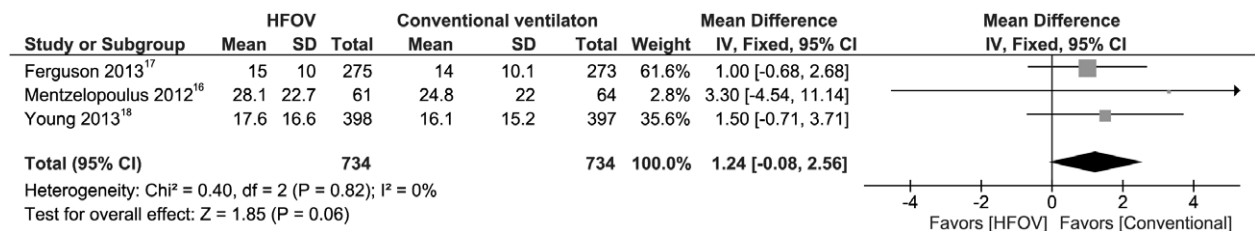

Fig. 5. Forest plot showing mean difference of duration of intensive care unit stay at individual study level and at pooled analysis level. HFOV = high-frequency oscillatory ventilation; IV fixed = inverse variance fixed model.

A pooled analysis at day 1, day 2, and day 3 found that mean airway pressure is similar between patients treated with HFOV and conventional ventilation. Mentzelopoulus *et al.*[16] reported similar mean airway pressure at day 5, but Ferguson *et al.*[17] reported significantly high mean airway pressure at day 7.

There was no significant difference in arterial carbon dioxide at different time points in between two groups. Arterial pH was statistically similar in the two groups at day 1 and day 2; a pooled analysis at day 3 showed a significantly low pH (MD, 0.03; 95% CI, 0.00 to 0.05; *P* = 0.03; inverse variance random) in patients received HFOV. However, the clinical importance of this minute difference is insignificant. A pooled analysis was possible at day 1 for P/F ratio and OI, which revealed a similar P/F ratio (MD, 10.12; 95% CI, –44.56 to 64.80; *P* = 0.72; inverse variance random) but a higher OI with HFOV (MD, 6.67; 95% CI, 3.67 to 9.67; *P* < 0.0001; inverse variance fixed). A random model of analysis for OI also found similar results (MD, 6.94; 95% CI, 3.17 to 10.71; *P* = 0.0003; inverse variance random).

Complications. A pooled analysis (n = 1,451) found that incidence of barotrauma is similar between the two groups

(risk ratio, 1.17; 95% CI, 0.87 to 1.58; *P* = 0.30; M-H fixed; fig. 7). A random-effect model also found similar result (risk ratio, 1.18; 95% CI, 0.87 to 1.59; *P* = 0.29; M-H random). Requirement of treatment crossover was similar in both the groups (risk ratio, 0.77; 95% CI, 0.44 to 1.34; *P* = 0.35; M-H fixed). Random-effect model also found similar results (risk ratio, 0.80; 95% CI, 0.43 to 1.48; *P* = 0.48; M-H random). Incidence of refractory hypoxemia is significantly less (risk ratio, 0.60; 95% CI, 0.39 to 0.93; *P* = 0.02; M-H fixed; fig. 8) with the use of HFOV. M-H random-effect model also found identical results (risk ratio, 0.60; 95% CI, 0.38 to 0.93; *P* = 0.02; M-H random). Incidence of refractory hypotension was found to be similar in the two groups (risk ratio, 1.25; 95% CI, 0.64 to 2.43; *P* = 0.52; M-H fixed). Random-effect model also found similar results (risk ratio, 1.33; 95% CI, 0.67 to 2.62; *P* = 0.41; M-H random).

Discussion

The principal finding of our meta-analysis is that HFOV does not confer any in-hospital mortality benefit over conventional lung-protective ventilation strategy in ARDS. Moreover, it is associated with a longer duration of mechanical
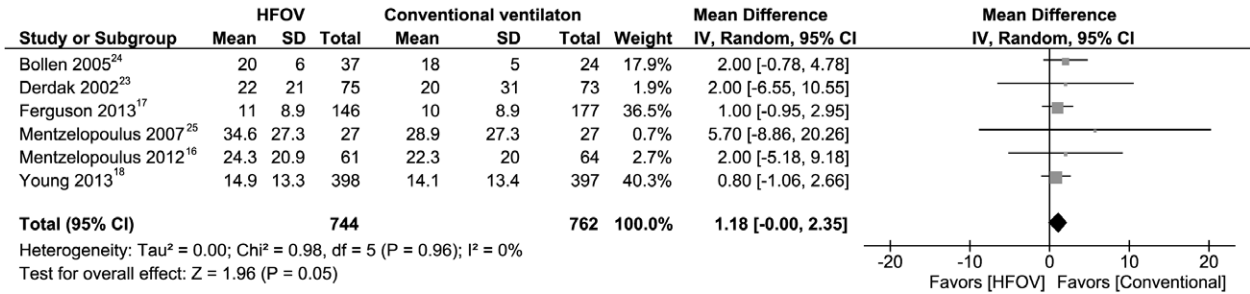
Study or Subgroup	HFOV			Conventional ventilaton			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Bollen 2005[24]	20	6	37	18	5	24	17.9%	2.00 [-0.78, 4.78]	
Derdak 2002[23]	22	21	75	20	31	73	1.9%	2.00 [-6.55, 10.55]	
Ferguson 2013[17]	11	8.9	146	10	8.9	177	36.5%	1.00 [-0.95, 2.95]	
Mentzelopoulus 2007[25]	34.6	27.3	27	28.9	27.3	27	0.7%	5.70 [-8.86, 20.26]	
Mentzelopoulus 2012[16]	24.3	20.9	61	22.3	20	64	2.7%	2.00 [-5.18, 9.18]	
Young 2013[18]	14.9	13.3	398	14.1	13.4	397	40.3%	0.80 [-1.06, 2.66]	
Total (95% CI)			**744**			**762**	**100.0%**	**1.18 [-0.00, 2.35]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 5 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)

Favors [HFOV]   Favors [Conventional]

Fig. 6. Forest plot showing mean duration of duration of mechanical ventilation at individual study level and at pooled analysis level. HFOV = high-frequency oscillatory ventilation; IV fixed = inverse variance fixed model.
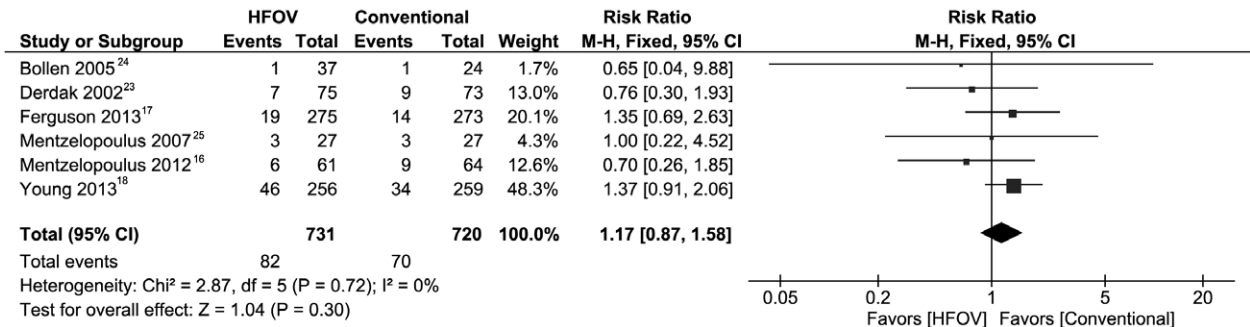
Study or Subgroup	HFOV		Conventional		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Bollen 2005[24]	1	37	1	24	1.7%	0.65 [0.04, 9.88]	
Derdak 2002[23]	7	75	9	73	13.0%	0.76 [0.30, 1.93]	
Ferguson 2013[17]	19	275	14	273	20.1%	1.35 [0.69, 2.63]	
Mentzelopoulus 2007[25]	3	27	3	27	4.3%	1.00 [0.22, 4.52]	
Mentzelopoulus 2012[16]	6	61	9	64	12.6%	0.70 [0.26, 1.85]	
Young 2013[18]	46	256	34	259	48.3%	1.37 [0.91, 2.06]	
Total (95% CI)		**731**		**720**	**100.0%**	**1.17 [0.87, 1.58]**	
Total events	82		70				

Heterogeneity: Chi² = 2.87, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

Favors [HFOV]   Favors [Conventional]

Fig. 7. Forest plot showing risk ratio of barotrauma from intervention at individual study level and at pooled analysis level. HFOV = high-frequency oscillatory ventilation; M-H fixed = Mantel–Haenszel fixed model.

ventilation. Duration of ICU stay is also prolonged with HFOV use although statistical significance has not been reached. Requirement of vasopressors/inotropes and neuro-muscular-blocking drugs was similar between HFOV and conventional ventilation management. HFOV improves indices of oxygenation (P/F ratio and OI) at least 1 day after initiation of therapy, and use of HFOV is not associated with barotrauma, hypotension, or treatment crossover and it reduces the incidence of refractory hypoxemia in comparison with conventional ventilation.

A previous meta-analysis[14] and a Cochrane review[15] by the same authors reported a significant in-hospital mortality benefit from the use of high-frequency ventilation in adult patients with ARDS. However, they could include only 365 patients. Two most recent multicenter trials published in 2013 reported different findings from the previous analysis. Ferguson et al.[17] reported a higher in-hospital mortality and Young et al.[18] reported equal mortality with the use of HFOV in patients with ARDS. Exclusion of these two studies echoes the results of the previous meta-analyses. Ferguson et al.[17] opined that as they used lung-protective ventilation strategy rigorously, HFOV failed to provide any benefit over conventional ventilation. Young et al.[18] also reported no benefit of HFOV in their trial; they said that use of Novalung R100 (Novalung Vision α; Hechingen, Germany) ventilator, which uses a pneumatically driven diaphragm with a fixed 1:1 I: E ratio, in their trial as opposed to SensorMedics 3100B (CareFusion, Yorba Linda, CA) ventilator, which uses an electromechanically

operated diaphragm at 1:2 IE ratio, may be responsible for this result. However, this is an unlikely phenomenon, as Ferguson et al.[17] also used Sensor Medics 3100B ventilator and reported an increased mortality with HFOV. Most important limitation of the study by Young et al.[18] is that they did not use mandatory lung-protective ventilation strategy in the control group; rather, they followed local protocol of the participating ICU. They only encouraged the participating units "to use pressure-controlled ventilation at 6 to 8 ml/kg of ideal body weight and to use the combinations of positive end-expiratory pressure and F_{IO_2} values that were used in the Acute Respiratory Distress Syndrome Network study." Consequently, exhaled tidal volume in the patients belonging to conventional group in that study is 8.3 ± 2.9 ml/kg (mean ± SD) of ideal body weight in first 24 h after randomization. Ferguson et al.[17] terminated their study prematurely because of an increased mortality with the use of HFOV even though the predefined stopping thresholds were not reached. They also used a relatively higher mean airway pressure in HFOV group; use of a lower mean airway pressure, different inspiratory and expiratory ratios, and oscillations could have changed their outcome.

Although we did not find any increase in the mortality with the use of HFOV, subsequent trials may also change our findings because a large well-designed RCT[17] has already found more harm with the use of HFOV.

We speculated that the rigorous use of lung-protective ventilation strategy might also be a reason for lack of further benefit of HFOV. However, a subgroup analysis failed to find
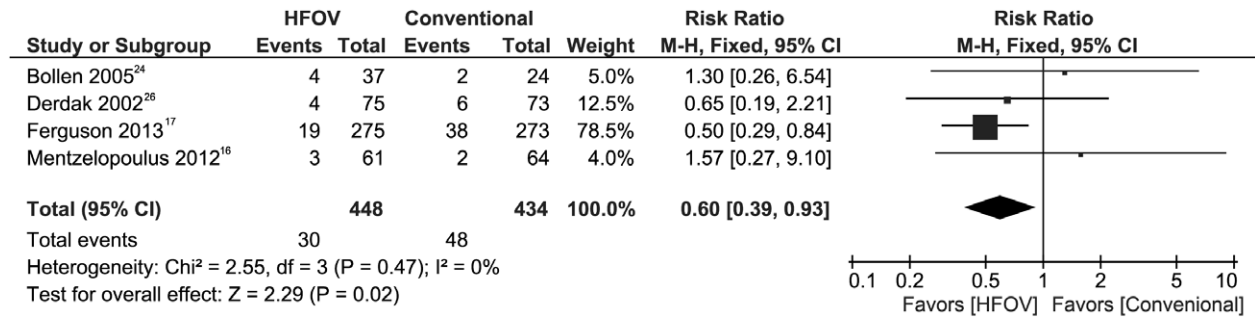
Fig. 8. Forest plot showing risk ratio of refractory hypoxemia at individual study level and pooled analysis. HFOV = high-frequency oscillatory ventilation; M-H fixed = Mantel–Haenszel fixed model.

any benefit of HFOV irrespective of whether a mandatory lung-protective strategy was used or not. However, in studies where a mandatory lung-protective strategy was not used, patients might have received variable tidal volume ventilation; that is, some of the patients might have received low-tidal-volume ventilation also. The mean ± SD tidal volume received by the patients in conventional ventilation group in first 24h after randomization as follows: 8.3 ± 2.9 ml/kg of ideal body weight (Young *et al.*[18]), 8.8 ± 1.6 ml/kg of ideal body weight (Bollen *et al.*[24]), and 8 ± 2 ml/kg of ideal body weight (Derdak *et al.*[23]).

It is worth mentioning that only two trials included in our analysis used recruitment maneuver and one of them also used tracheal gas insufflation along with HFOV. Tracheal gas insufflation along with HFOV improves oxygenation[29] and widespread use of it may improve outcome in the future. A higher mean airway pressure with HFOV may impair right ventricular function and hence contribute to hemodynamic compromise[30] and ultimately poor oxygenation and outcome. Again, the HFOV protocol varied in various studies and various authors used HFOV for different periods of time. Probably, Fessler *et al.*[31] aptly concluded that the use of more consistent protocol may improve outcome with HFOV use. Use of prone position along with high-frequency ventilation may be another technique for improving oxygenation and reducing inflammation[32] which has also not been applied in most of the RCTs. Experimental animal studies[33] also showed an improved survival with HFOV in experimental lung injury model principally because of a lower tidal volume.[34] Duration of mechanical ventilation is also prolonged with the use of HFOV. Although all the studies used predefined weaning protocol, there was no uniformity in the protocols of weaning; hence, these should be interpreted with caution.

Long-term/6-month mortality has been reported only in two trials[16,23] and a beneficial effect of HFOV has been found on it. However, none of the two large trials, which significantly influenced the result of the analysis, reported long-term mortality.

Time of institution of HFOV is also an important determinant of survival. Duration of conventional ventilation before HFOV is an independent predictor of mortality in several

observational and retrospective studies.[10–13] A meta-analysis found that duration of ventilation before starting HFOV differed significantly between survivors and nonsurvivors.[35] Primary cause of ARDS may also influence the success of HFOV. Pachl *et al.*[36] found that HFOV is beneficial in improving oxygenation parameters only in patients with extra pulmonary cause of ARDS. Presence of more recruitable lung tissue may be the cause of success of HFOV in these patients.[37]

Despite lacking mortality benefit, HFOV consistently improved parameters of oxygenation and previous studies also reported similar findings. We found a less incidence of refractory hypoxemia with the use of HFOV. Another important finding of our study is that HFOV does not increase the incidence of barotrauma, which is consistent with the findings of the previous meta-analysis. A higher mean airway pressure during conventional ventilation is believed to cause harm to the lung[38]; however, during HFOV, the mean airway pressure does not correlate with the alveolar pressure,[14] which is a more important determinant of lung injury in ARDS. Because the mean airway pressures measured in the trachea during high-frequency oscillation is lower than the value displayed on the ventilator, a comparison of mean airway pressure and OI does not seem logical between HFOV and conventional ventilation.

Presently, it is unknown whether HFOV improves outcome when applied as a rescue strategy rather than the primary ventilation strategy. Hence, potential opportunity for research exists in this gray area. Moreover, whether other therapeutic interventions, such as recruitment maneuvers, tracheal gas insufflations, and prone positioning, influence outcome when used along with HFOV needs to be addressed. Recently, continuous positive airway pressure/assisted spontaneous breathing has been used along with high-frequency ventilation in patients with ARDS due to H1N1 influenza.[39] Again, ARDS is a heterogeneous entity, and HFOV may have a different impact on ARDS due to lung pathology and nonlung pathology. Therefore, large multicentric trials are required to establish the exact role of HFOV in ARDS.

Limitations
As with other meta-analyses, our review is also prone to biases. We did not ask the authors of the included trials

for unpublished data and did not include ongoing trials. The protocol of HFOV used in different studies is variable; hence, possibilities of biases are there. Two recent large multicentric studies influenced the primary outcome significantly. As both of these studies were multicentric, probability of heterogeneity in study protocol exists. The largest study did not mandate use of "lung protective strategy" in the control group and used a ventilator with a different mechanism. Our result may change with the publication of further large RCTs. The inclusion criteria and patient population are also variable in different studies. The primary cause of ARDS may influence ultimate outcome. Timings of initiation of HFOV and duration of treatment may also influence mortality.

Conclusion

Our meta-analysis does not support routine use of high-frequency ventilation in place of conventional "lung-protective strategy" ventilation in adult patients with ARDS as there is no mortality benefit; on the contrary, the duration of mechanical ventilation as well as ICU stay may even be increased. We look forward to further research to find out the role of HFOV as rescue therapy in refractory hypoxemia in patients with ARDS.

Acknowledgments

Competing Interests

The authors declare no competing interests.

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Appendix. Details of PubMed Search Strategy

high[All Fields] AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "frequency"[All Fields] OR "epidemiology"[MeSH Terms] OR "frequency"[All Fields]) AND oscillatory[All Fields] AND ("ventilation"[MeSH Terms] OR "ventilation"[All Fields] OR "respiration"[MeSH Terms] OR "respiration"[All Fields]) AND ards[All Fields]

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