ORIGINAL ARTICLE

Severity of Hypoxemia and Effect of High-Frequency Oscillatory Ventilation in Acute Respiratory Distress Syndrome

Maureen O. Meade[1,2], Duncan Young[3], Steven Hanna[1,2], Qi Zhou[1,2], Thomas E. Bachman[4], Casper Bollen[5], Arthur S. Slutsky[6,7,8], Sarah E. Lamb[3], Neill K. J. Adhikari[6,8,9], Spyros D. Mentzelopoulos[10], Deborah J. Cook[1,2], Sachin Sud[11], Roy G. Brower[12], B. Taylor Thompson[13], Sanjoy Shah[14], Alex Stenzler[15], Gordon Guyatt[1,2], and Niall D. Ferguson[6,8,16,17]

[1]Department of Medicine and [2]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada; [3]University of Oxford, Oxford, United Kingdom; [4]Czech Technical University–Prague, Kladno, Czech Republic; [5]Wilhelmina Children's Hospital, Utrecht, the Netherlands; [6]Interdepartmental Division of Critical Care Medicine, [8]Department of Medicine, and [16]Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada; [7]Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada; [9]Department of Critical Care Medicine, Sunnybrook Health Science Centre, Toronto, Canada; [10]Athens Medical School, Evaggelismos General Hospital, Athens, Greece; [11]Trillium Health Partners, University of Toronto, Mississauga, Ontario, Canada; [12]Johns Hopkins University School of Medicine, Baltimore, Maryland; [13]Harvard University, Boston, Massachusetts; [14]University Hospitals Bristol, National Health Service Foundation Trust, Bristol, United Kingdom; [15]12th Man Technologies, Garden Grove, California; and [17]Division of Respirology, Department of Medicine, University Health Network and Mount Sinai Hospital, Toronto General Research Institute, Toronto, Canada

ORCID ID: 0000-0002-6213-5264 (N.D.F.).

Abstract

Rationale: High-frequency oscillatory ventilation (HFOV) is theoretically beneficial for lung protection, but the results of clinical trials are inconsistent, with study-level meta-analyses suggesting no significant effect on mortality.

Objectives: The aim of this individual patient data meta-analysis was to identify acute respiratory distress syndrome (ARDS) patient subgroups with differential outcomes from HFOV.

Methods: After a comprehensive search for trials, two reviewers independently identified randomized trials comparing HFOV with conventional ventilation for adults with ARDS. Prespecified effect modifiers were tested using multivariable hierarchical logistic regression models, adjusting for important prognostic factors and clustering effects.

Measurements and Main Results: Data from 1,552 patients in four trials were analyzed, applying uniform definitions for study variables and outcomes. Patients had a mean baseline Pa_{O_2}/FI_{O_2} of 114 ± 39 mm Hg; 40% had severe ARDS (Pa_{O_2}/FI_{O_2} <100 mm Hg). Mortality at 30 days was 321 of 785 (40.9%) for HFOV patients versus 288 of 767 (37.6%) for control subjects (adjusted odds ratio, 1.17; 95% confidence interval, 0.94–1.46; $P = 0.16$). This treatment effect varied, however, depending on baseline severity of hypoxemia ($P = 0.0003$), with harm increasing with Pa_{O_2}/FI_{O_2} among patients with mild-moderate ARDS, and the possibility of decreased mortality in patients with very severe ARDS. Compliance and body mass index did not modify the treatment effect. HFOV increased barotrauma risk compared with conventional ventilation (adjusted odds ratio, 1.75; 95% confidence interval, 1.04–2.96; $P = 0.04$).

Conclusions: HFOV increases mortality for most patients with ARDS but may improve survival among patients with severe hypoxemia on conventional mechanical ventilation.

Keywords: high-frequency oscillatory ventilation; acute respiratory distress syndrome; mechanical ventilation

(Received in original form September 26, 2016; accepted in final form February 24, 2017)

Supported by Canadian Institutes of Health Research.

Author Contributions: M.O.M., D.Y., S.H., Q.Z., T.E.B., C.B., A.S.S., S.E.L., N.K.J.A., S.D.M., D.J.C., S. Sud, R.G.B., B.T.T., S. Shah, A.S., G.G., and N.D.F. contributed to the study design and analysis plan, interpreted the data, and revised the manuscript for important intellectual content. M.O.M. (principal investigator) drafted the manuscript. M.O.M. and Q.Z. (study analyst) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Correspondence and requests for reprints should be addressed to Niall D. Ferguson, M.D., M.Sc., Toronto General Hospital, 585 University Avenue, 11-PMB-120, Toronto, ON M5G 2N2, Canada. E-mail: n.ferguson@utoronto.ca

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 196, Iss 6, pp 727–733, Sep 15, 2017

Originally Published in Press as DOI: 10.1164/rccm.201609-1938OC on February 28, 2017
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: High-frequency oscillatory ventilation (HFOV) is theoretically lung protective in acute respiratory distress syndrome (ARDS), but results of clinical trials are inconsistent, with study-level meta-analyses suggesting no effect on mortality.

What This Study Adds to the Field: We found a convincing relationship between severity of ARDS and impact of therapy: HFOV was harmful in patients with moderate ARDS, whereas showing possible benefit in patients with severe hypoxemia. This heterogeneity of treatment effect implies that HFOV should be avoided in mild and moderate ARDS. Clinicians might consider HFOV in patients with severe ARDS who remain hypoxic after optimizing conventional lung-protective ventilation and for whom other approaches (e.g., proning, extracorporeal support) are either contraindicated or unavailable.

Acute respiratory distress syndrome (ARDS) is a common complication of critical illness and mechanical ventilation is often essential to preserve life. Because mechanical ventilation is intrinsically harmful to lung tissue, protecting the lungs from iatrogenic ventilator-induced injury is central to the care of critically ill patients with ARDS.

Lung-protective strategies, such as low tidal volume ventilation and prone positioning, can reduce cyclic overdistention of lung units and improve survival (1). Another technique that has lung-protective potential is high-frequency oscillatory ventilation (HFOV). In contrast to conventional lung-protective ventilation in which tidal volumes range from 4 to 8 ml/kg predicted body weight, HFOV delivers very small volumes (~1–3 ml/kg) at very high rates (3–10 oscillations/s). In adults, clinicians initially applied HFOV in patients with intractable hypoxemia during ARDS (2). Over time, however, HFOV was initiated with relatively less severe ARDS (3).

A review of four early randomized trials detected a statistically significant survival benefit with HFOV compared with conventional ventilation (4). Two subsequent large trials found no effect, or increased mortality with HFOV (5, 6). When combined in conventional meta-analyses the results suggest no significant effect of HFOV on mortality compared with conventional ventilation (7). The design of these six trials in adult ARDS varied in ways that might explain their divergent results, and in addition it is possible that heterogeneity of HFOV treatment effect varies across subgroups. We assembled individual patient data from existing randomized trials to elucidate the effects of HFOV on ARDS mortality after controlling for potentially confounding factors (8). In addition, we investigated three patient variables as HFOV effect modifiers: (*1*) baseline oxygenation, (*2*) respiratory system compliance, and (*3*) body mass index.

Methods

A complete description of the study methods is available in the online supplement.

Literature Search and Study Selection

We included randomized trials comparing HFOV with conventional ventilation among adults with ARDS; we excluded trials in which the HFOV protocol incorporated a secondary intervention. Two reviewers independently searched for eligible studies and resolved disagreements by consensus. We excluded one trial that applied HFOV for multiple short periods (9), and a second trial that did not capture key variables (10). We included four multicenter trials originating in the United States (MOAT [Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial]; n = 148) (11), Netherlands (EMOAT [European Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial]; n = 61) (10), United Kingdom (OSCAR [Oscillation in ARDS]; n = 795) (6), and Canada (OSCILLATE [Oscillation for ARDS Treated Early]; n = 548) (5).

Database Development

We generated a standardized database for each trial, with uniform data definitions and including as many variables as possible. To harmonize data, we retrospectively collected Acute Physiology and Chronic Health Evaluation (APACHE II) (12) scores at intensive care unit admission for 527 of 548 (96%) participants in the OSCILLATE trial (5). Other missing variables were derived from existing variables; full details are available in the online supplement (*see* Appendices E1–E6).

Analysis of Patient Outcomes and Subgroups

Base model. We compared HFOV with conventional ventilation on the primary outcome of 30-day mortality, the longest follow-up common to all trials. We used mixed-effects logistic regression multilevel modeling that accounted for clustering of individual outcomes within treatment centers and within studies. We adjusted for three prognostic variables (age, APACHE II score, and baseline duration of ventilation) using fixed effects.

Subgroup analyses. To determine if the effect of HFOV on 30-day mortality differed across subgroups, we prespecified three patient variables as potential effect modifiers: (*1*) $Pa_{O_2}/F_{I_{O_2}}$, (*2*) estimated respiratory system compliance (*see* Appendix E2), and (*3*) body mass index (*see* Appendix E3). We entered these variables separately into the base model as fixed effects and tested for an interaction with treatment.

Other analyses. We explored the hypothesis that HFOV may be superior to traditional high tidal volume ventilation strategies but inferior to low tidal volume ventilation. We could not analyze tidal volume as a patient variable because HFOV patients did not have tidal volume measurements; therefore, we approached tidal volume as a hospital variable. We reasoned that the average tidal volume on study Day 1 in each hospital could reflect, to some degree, the average lung protection used for study patients at each hospital, recognizing the limitations that this is a post-randomization variable, it assumes a homogeneous treatment of all control patients at a given hospital, and it is confounded by severity of lung injury. For each hospital, among control group patients only, we determined the average tidal volume (measured in ml/kg predicted body weight) (*see* Appendix E1) on the first day after randomization

(*see* Appendix E5). We added this variable into our primary model as a hospital variable, controlling for patient Pa_{O_2}/FI_{O_2}.

We also explored the hypothesis that more experience with study-specific HFOV protocols would lead to improved mortality among patients randomized to HFOV. We tested for this association, comparing mortality by quartile of enrolment order among patients randomized to the HFOV arm in each center. We again used mixed-effects logistic regression, adjusting for trial, age, APACHE II score, and duration of mechanical ventilation before enrolment. We also addressed the impact of HFOV on new-onset barotrauma (*see* Appendix E6). The mixed-effects logistic regression model accounted for clustering within trials and hospitals as described previously, plus one adjustment variable, baseline Pa_{O_2}/FI_{O_2}, as a fixed effect. We assessed for three potential effect modifiers on the effect of HFOV on barotrauma: (*1*) Pa_{O_2}/FI_{O_2}, (*2*) respiratory system compliance, and (*3*) body mass index. Analysts used Stata version 8.2 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The four trials in this study (Table 1) included 1,552 patients of whom 1,327 (86%) had complete data for every regression analysis. The OSCILLATE trial uniquely mandated a low tidal volume, high positive end-expiratory pressure (PEEP), conventional ventilation strategy for control group patients. The OSCAR and OSCILLATE trials applied high oscillation frequencies to minimize tidal volumes (13). No trials used protocols for sedation or neuromuscular blockade.

In the combined database, the two groups had similar baseline prognosis (Table 2). Lung injury was relatively severe, with a mean Pa_{O_2}/FI_{O_2} of 114 ± 39 mm Hg and an average PEEP of 12 ± 3 cm H_2O. Table 3 shows respiratory variables over the first 3 days of study. The mean (SD) duration of HFOV was 5.5 ± 4.8 days.

Therapeutic cointerventions varied across studies. In the two trials that recorded paralytic use, 39% of patients received this therapy, which did not differ between groups (5, 6). Prone ventilation was rare except in the OSCAR trial in which 10% of HFOV and 20% of control patients were proned. Only 95 patients (6%) received inhaled nitric oxide. Three studies allowed HFOV among control subjects in clearly defined settings of intractable hypoxemia, acidosis, barotrauma, or hypotension (5, 10, 11). Rates of HFOV among control subjects were 18% (MOAT) (11), 12% (OSCILLATE, eMOAT) (5, 10), and 3% (OSCAR) (6).

Thirty-day mortality was 321 of 785 (40.9%) for HFOV versus 288 of 767 (37.6%) for control subjects. The adjusted odds ratio (OR) was 1.17 (95% confidence interval [CI], 0.94–1.46; $P = 0.16$; patients with missing outcome or adjustment data, 4.7%). The Hosmer-Lemeshow test indicated adequate goodness-of-fit ($P = 0.83$).

Table 1. Characteristics of Included Trials

Characteristic	MOAT2, 2002	EMOAT, 2005	OSCILLATE, 2013	OSCAR, 2013
Countries participating	United States, Canada	United Kingdom, France, Germany	Canada, United States, Saudi Arabia, Chile, India, Mexico, United Kingdom	United Kingdom
Inclusion Pa_{O_2}/FI_{O_2}	<200	<200	<200	<200
Recruitment period	1997–2000	1997–2001	2007–2008; 2009–2012*	2007–2012
No. of hospitals	10	4	41	30
HFOV:control sample size	75:73	37:24	275:273	398:397
Risk of bias				
Concealed allocation	Yes	Yes	Yes	Yes
Complete follow-up	100%	95%	100%	100%
Blinding of clinical staff	No	No	No	No
Early stopping (reason)	No	Yes (slow recruitment)	Yes (evidence of harm)	No
HFO ventilation				
Machine	3100B†	3100B	3100B	R100‡
Initial mPaw, cm H_2O	mPaw on CV +5 cm H_2O	mPaw on CV +5 cm H_2O	30 cm H_2O	Pplat on CV +5 cm H_2O
Frequency	5 Hz at initiation	5 Hz at initiation	Highest possible with pH>7.25	Highest possible with pH>7.25
Recruitment maneuvers	No	No	Yes	No
Conventional ventilation				
Preferred mode	Pressure control	Pressure control	Pressure control	Pressure control
Tidal volume protocol	6–10 ml/kg	PIP ≤45 cm H_2O	4–8 ml/kg PBW mandated	6–8 ml/kg PBW suggested
PEEP protocol	10–18 cm H_2O	Not specified	High PEEP mandated	Lower PEEP suggested
Recruitment maneuvers	No	No	Yes	No

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CV = conventional ventilation; EMOAT = European Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial; HFOV = high-frequency oscillatory ventilation; MOAT2 = Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial; mPaw = mean airway pressure; OSCAR = Oscillation in ARDS trial; OSCILLATE = Oscillation for ARDS Treated Early trial; Pa_{O_2}/FI_{O_2} = partial pressure of arterial oxygen:inspired fraction of oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure.

*Initial 12-center pilot phase with 1-year hiatus before full trial.

†SensorMedics (Yorba Linda, CA).

‡Metran Corporation (Kawaguchi, Japan).

Table 2. Patient Characteristics at Baseline*

Characteristic	HFOV (*n* = 785)	Control (*n* = 767)	Missing (%)
Age, yr	54 ± 17	54 ± 17	0.2
Male sex, n (%)	492 (63)	451 (59)	0
APACHE II score†	23 ± 8	24 ± 8	2.6
Duration of mechanical ventilation, d, median (IQR)	2 (1–4)	2 (1–3)	0
Pneumonia, n (%)	430 (55)	418 (55)	0
Aspiration, n (%)	80 (11)	83 (12)	9.5
Barotrauma, n (%)	53 (7)	41 (5)	1.2
Respiratory measures			
Pa_{O_2}/FI_{O_2}, mm Hg	114 ± 38	115 ± 40	2.0
Pa_{O_2}/FI_{O_2} ⩽100 mm Hg, n (%)	299 (39)	298 (39)	2.0
FI_{O_2}	0.74 ± 0.18	0.73 ± 0.17	1.5
Pa_{O_2}, mm Hg	79 ± 21	80 ± 23	1.8
Set PEEP, cm H_2O	12 ± 4	13 ± 4	2.6
Plateau pressure, cm H_2O	32 ± 8	32 ± 9	4.6
Tidal volume, ml/kg of predicted body weight	8.0 ± 2.7	7.8 ± 2.5	5.0
Respiratory rate, breaths/min	23 ± 7	23 ± 7	9.9
Prone positioning, n (%)	27 (4)	26 (4)	9.5
Inhaled nitric oxide, n (%)	31 (4)	25 (4)	9.5

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HFOV = high-frequency oscillatory ventilation; IQR = interquartile range; Pa_{O_2}/FI_{O_2} = partial pressure of arterial oxygen:inspired fraction of oxygen; PEEP = positive end-expiratory pressure.
*Plus-minus values are means ± SD. Data exclude imputations for missing data.
†Scores on APACHE II range from 0 to 71, with higher scores indicating greater severity of illness.

We found a statistically significant interaction between baseline Pa_{O_2}/FI_{O_2} and the effect of HFOV ($P = 0.0003$), with increasing harm from HFOV at higher values of Pa_{O_2}/FI_{O_2}. The exact threshold at which the effect of HFOV changes from harm to benefit, if such a threshold exists, is less certain (Figure 1). The line of best fit crosses an OR of 1.0 at a Pa_{O_2}/FI_{O_2} value close to 100 mm Hg (95% CI, 64–117). To test the robustness of this statistical model, we applied these thresholds in a *post hoc* analysis. In 614 patients with Pa_{O_2}/FI_{O_2} 100 mm Hg or less the OR for mortality with HFOV was 0.83 (95% CI, 0.58–1.19; $P = 0.30$), adjusted for trial, age, APACHE II score, and duration of mechanical ventilation before enrolment; in 140 patients with Pa_{O_2}/FI_{O_2} 64 mm Hg or less, the adjusted OR was 0.68 (95% CI, 0.3–1.50; $P = 0.34$).

Table 3. Respiratory Variables During First 3 Days of Treatment

Variable	Day 1*			Day 2			Day 3		
	HFOV	Control	*P* Value	HFOV	Control	*P* Value	HFOV	Control	*P* Value
Pa_{O_2}/FI_{O_2}, mm Hg	177 (71) n = 741	161 (75) n = 740	<0.0001	193 (73) n = 671	170 (68) n = 703	<0.0001	194 (70) n = 567	175 (71) n = 658	<0.0001
FI_{O2}	0.54 (0.20) n = 742	0.57 (0.19) n = 747	0.01	0.47 (0.16) n = 675	0.56 (0.18) n = 711	0.07	0.45 (0.15) n = 573	0.50 (0.17) n = 671	<0.0001
Pa_{O_2}, mm Hg	88 (37) n = 741	83 (34) n = 742	0.01	83 (27) n = 674	79 (20) n = 705	0.001	81 (26) n = 568	80 (22) n = 658	0.63
Pa_{CO_2}, mm Hg	52 (16) n = 742	48 (12) n = 740	<0.0001	53 (16) n = 673	47 (12) n = 705	<0.0001	52 (16) n = 568	47 (13) n = 657	<0.0001
Arterial pH	7.31 (0.1) n = 740	7.34 (0.1) n = 735	<0.0001	7.32 (0.09) n = 675	7.36 (0.10) n = 697	<0.0001	7.34 (0.09) n = 568	7.38 (0.09) n = 651	<0.0001
Mean airway pressure, cm H_2O	28 (6) n = 739	22 (6) n = 350†	<0.0001	26 (6) n = 672	20 (6) n = 334*	<0.0001	25 (7) n = 563	20 (7) n = 319*	<0.0001
PEEP, cm H_2O		13 (4) n = 725			14 (5) n = 690			12 (4) n = 646	
Plateau pressure, cm H_2O		30 (9) n = 686			29 (9) n = 650			28 (10) n = 595	
Tidal volume, ml/kg of predicted body weight		7.6 (2.3) n = 705			7.7 (2.4) n = 678			7.9 (2.8) n = 636	

Definition of abbreviations: HFOV = high-frequency oscillatory ventilation; PEEP = positive end-expiratory pressure.
*Day 1 data correspond to data on the morning of the day after randomization.
†Mean airway pressures not recorded for conventional ventilation patients in the OSCAR trial.

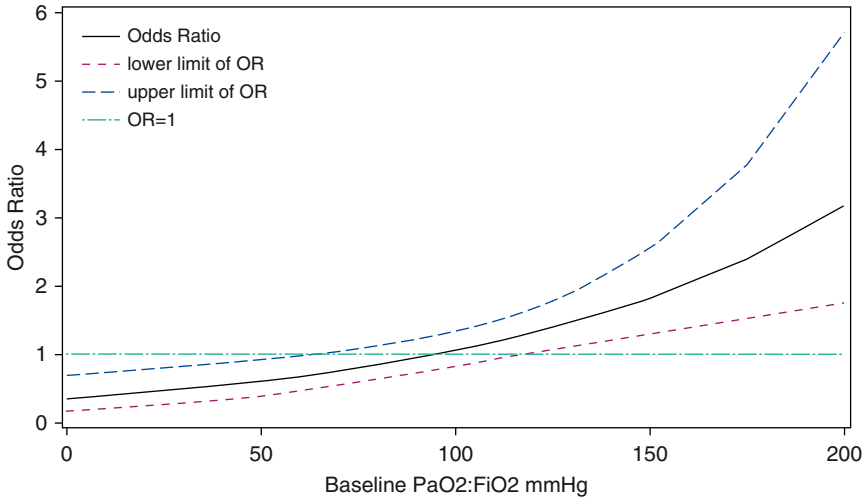

Figure 1. Interaction between severity of lung injury and treatment effect of high-frequency oscillatory ventilation (HFOV). Changing odds ratio (OR) (*black line*) along with 95% confidence intervals (*blue* and *magenta dashed lines*) for the treatment effect of HFOV versus conventional ventilation across the range of baseline Pa_{O_2}/FI_{O_2} ratio. An OR greater than 1 denotes increased 30-day mortality with HFOV compared with conventional ventilation.

We found no interaction with respiratory system compliance ($P = 0.35$) or body mass index ($P = 0.34$) on the mortality effect of HFOV. We found a weak interaction between treatment effect and the degree of low tidal volume ventilation at participating hospitals (interaction $P = 0.08$). The direction of this trend suggested greater harm from HFOV versus conventional ventilation in hospitals with lowest tidal volumes during conventional ventilation. For the lowest quartile of tidal volume (<6.29 ml/kg predicted body weight) the OR for HFOV versus conventional ventilation was 1.92 (95% CI, 1.18–3.13; $P = 0.01$), whereas the three other quartiles showed no significant differences.

Contrary to our prediction, survival was better among earlier quartiles of HFOV patients in each hospital when compared with later patients (Table 4) ($P \leqslant 0.02$), with a clear dose–response relationship. We tested the robustness of this unexpected association and found that it was consistent in the three largest trials, it was preserved after adjusting for the total number of patients at each hospital, and preserved when we restricted the analysis to hospitals enrolling greater than 10 patients. In a similar analysis among control patients there was no equivalent finding of an association between hospital experience and survival ($P = 0.37$).

The overall risk of barotrauma was 98 of 1,458 (7%) and the odds of barotrauma were higher with HFOV (adjusted OR, 1.87; 95% CI, 1.06–3.28; $P = 0.03$). In the sensitivity analysis excluding the OSCAR trial, results were similar (OR, 1.71; 95% CI, 1.11–2.26; $P = 0.01$). Neither Pa_{O_2}/FI_{O_2}, body mass index, nor estimated respiratory system compliance interacted significantly with treatment effect ($P = 0.06$, $P = 0.10$, and $P = 0.24$, respectively).

Table 4. Relationship between Mortality in HFOV Patients and Hospital Experience with Study Protocols for HFOV

	Successive Patients within Each Quartile	Mortality (95% CI)	*P* Value
First quartile	1st–3rd	36% (28–45)	<0.02
Second quartile	4th–6th	41% (32–51)	
Third quartile	7th–12th	49% (39–58)	
Fourth quartile	13th–final	53% (42–64)	

Definition of abbreviations: CI = confidence interval; HFOV = high-frequency oscillatory ventilation. Patients assigned to HFOV. Patients are grouped into quartiles according to their chronologic order of randomization to HFOV at participating hospitals. Mortality rates are adjusted for age, Acute Physiology and Chronic Health Evaluation II score, baseline Pa_{O_2}/FI_{O_2}, and duration of mechanical ventilation before enrollment.

Discussion

The purpose of this study was to reconcile disparate results of clinical trials of HFOV in adults with ARDS, using individual patient data to examine possible subgroup effects where certain patients might benefit or be harmed by HFOV. We found a convincing relationship between severity of ARDS and responsiveness to therapy: HFOV seems harmful for most patients with ARDS and possibly beneficial in those with severe alterations in gas exchange. This heterogeneity of treatment effect implies that, contrary to conventional study-level meta-analyses that suggest no net benefit or harm from HFOV, individual adults with ARDS may be harmed or helped with HFOV depending largely on their baseline severity of lung injury as judged by Pa_{O_2}/FI_{O_2} ratio.

Several features support the credibility of a different effect of HFOV in patients with more severe compared with less severe ARDS. The direction of effect was consistent with an *a priori* hypothesis, it was apparent within all studies, it was one of a relatively small number of subgroup analyses, and it was supported by a very low *P* value in the test for interaction ($P = 0.0003$). Furthermore, this subgroup finding is consistent with other treatments in ARDS, such as prone position, paralytic agents, and relatively high PEEP (14, 15), which also seem to benefit only patients with lower Pa_{O_2}/FI_{O_2}.

The precise value of Pa_{O_2}/FI_{O_2} below which HFOV is beneficial is, however, less certain. The model suggests that HFOV is beneficial at low Pa_{O_2}/FI_{O_2} values, but unmeasured confounding factors could alter the threshold at which HFOV becomes beneficial. We did not identify a discrete subgroup based on Pa_{O_2}/FI_{O_2} that showed unequivocal statistically significant benefit from HFOV, although the point estimates for HFOV effectiveness in these under-powered subgroup comparisons were consistent with the effect modifier model results. We believe that among the possible Pa_{O_2}/FI_{O_2} thresholds that one might choose to use HFOV, levels below 64 mm Hg (the value at which the CI

around the line of best fit excludes an OR of 1.0) (Figure 1) are most reasonable.

Neither respiratory system compliance nor body mass index modified the effect of HFOV on mortality. Furthermore, our analysis provides only weak support for the hypothesis that diverging results across trials were related to diverging control ventilation strategies. This analysis of lung-protection has important limitations, however, because it assumes a fixed degree of lung protection for all control patients at a given hospital. In addition this was a post-randomization variable that may change not only with local practice but also severity of lung injury and a variety of factors other than local practice. Average low tidal volume may also be a marker of hospital quality in general. Nonetheless, when average tidal volumes in control patients were in the lowest quartile we did see a significant harm signal for HFOV. Thus it remains plausible that the harm signal from HFOV seen in most patients with ARDS was more apparent when HFOV was compared with current standards for lung protective low tidal volume ventilation, and obfuscated when compared with harmful conventional mechanical ventilation using large tidal volumes.

We did not find that patient outcomes improve with increasing experience in the application of a study HFOV protocol. Conversely, we found increasing harm associated with HFOV as more patients were enrolled in any given hospital. This finding was unexpected but robust, and did not seem related to changes in patient selection over time. There are several plausible hypotheses to explain this observation. Patient accrual within many hospitals might have been too slow to sustain the early level of training, expertise, and care, with a resultant decline in efficacy over time. Alternatively, or in addition, experience within a clinical trial is only a proxy for and may differ from overall clinical experience; this particular analysis does not address the amount of hospital HFOV experience before the study. Although this analysis may spur future investigations regarding the volume–outcome relationship with HFOV, we believe that it should *not* be interpreted as an endorsement to use HFOV only in low-volume centers. It does suggest that HFOV requires greater monitoring vigilance than conventional ventilation (16).

Strengths of this report include the advantages of individual patient data analyses, which allowed detailed evaluation of patient subgroups, adjustment for patient-level prognostic factors, and clustering within trials and hospitals. As the original trial investigators, we were also able to unify our *a priori* approach to study data, outcomes, and analyses, and complete patient-level data provided a high degree of analytic precision. This approach yielded different results than prior study-level meta-analyses, which found no overall effect of HFOV on survival or barotrauma (7, 17). The primary trials of this review had generally low risk of bias, their greatest threat being lack of caregiver blinding. We used multiple imputations as the most principled approach to a small amount of missing data (18). To avoid spurious findings, we limited the number of subgroup analyses. Supporting broad generalizability of our findings, these data derive from four trials, seven countries, and 85 hospitals with a range of prior HFOV experience.

This study has limitations. Most importantly, as a secondary analysis of randomized trial data, the ARDS severity subgroup finding is not as robust as would be generated by a new randomized trial of HFOV enrolling only patients with intractable hypoxemia. We are, however, unaware of any such trial underway or planned, and moreover such a trial would have major challenges in feasibility given the small number of eligible patients; thus, this individual patient data meta-analysis provides the most informative exploration of the issue at hand that is likely to ever be available. The potential for unknown confounders supports a conservative interpretation of our findings, and particularly the Pa_{O_2}/Fi_{O_2} threshold for consideration of HFOV. Notable potential confounders include different protocols for titrating mean airway pressure during HFOV or PEEP during conventional ventilation, and our inability to investigate these variables is another limitation of this review. Other limitations include the inability to investigate hemodynamic consequences of HFOV because of lack of reporting in some trials (16). In addition, some of our analyses may have been underpowered to detect existing effect modifiers, particularly the analyses of respiratory system compliance that relied on derivations from dynamic respiratory data from patients, some of whom were spontaneously breathing, rather than actual static compliance measurements.

Our findings have implications for clinical care. Among critically ill adults with ARDS, HFOV originated as a therapeutic option for those patients with refractory hypoxemia. Before the most recent completion of the two largest trials, clinical adoption of HFOV in adults had increased rapidly in many centers for relatively less severe hypoxemia (19). Our results suggest that this expansion of clinical indication should be reversed and HFOV generally should not be used for patients with mild or moderate ARDS. The results of this study also indicate that there remains a potential role for HFOV in a restricted subgroup of severe ARDS. In particular, clinicians caring for patients with severe hypoxia with ARDS and who have optimized conventional lung-protective ventilation might consider initiation of HFOV, especially when other approaches (e.g., proning, extracorporeal support) are contraindicated or unavailable. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Burns KEA, Adhikari NKJ, Slutsky AS, Guyatt GH, Villar J, Zhang H, Zhou Q, Cook DJ, Stewart TE, Meade MO. Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis. *PLoS One* 2011;6:e14623.
2. Fort P, Farmer C, Westerman J, Johannigman J, Beninati W, Dolan S, Derdak S. High-frequency oscillatory ventilation for adult respiratory distress syndrome: a pilot study. *Crit Care Med* 1997;25:937–947.
3. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K, Lamontagne F, *et al.*; Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009;302:1872–1879.

4. Sud S, Sud M, Friedrich JO, Meade MO, Ferguson ND, Wunsch H, Adhikari NKJ. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ* 2010;340:c2327.
5. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matté A, Walter SD, Lamontagne F, *et al*.; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795–805.
6. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH; OSCAR Study Group. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013;368: 806–813.
7. Sud S, Sud M, Friedrich JO, Wunsch H, Meade MO, Ferguson ND, Adhikari NK. High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2016;4:CD004085.
8. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685–1693.
9. Mentzelopoulos SD, Malachias S, Zintzaras E, Kokkoris S, Zakynthinos E, Makris D, Magira E, Markaki V, Roussos C, Zakynthinos SG. Intermittent recruitment with high-frequency oscillation/tracheal gas insufflation in acute respiratory distress syndrome. *Eur Respir J* 2012; 39:635–647.
10. Bollen CW, van Well GTJ, Sherry T, Beale RJ, Shah S, Findlay G, Monchi M, Chiche J-D, Weiler N, Uiterwaal CSPM, *et al*. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. *Crit Care* 2005;9: R430–R439.
11. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, Granton J; Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial (MOAT) Study Investigators. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med* 2002;166:801–808.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–829.
13. Hager DN, Fessler HE, Kaczka DW, Shanholtz CB, Fuld MK, Simon BA, Brower RG. Tidal volume delivery during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2007;35:1522–1529.
14. Alhazzani W, Alshahrani M, Jaeschke R, Forel J-M, Papazian L, Sevransky J, Meade MO. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013;17:R43.
15. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, *et al*. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.
16. Guervilly C, Forel J-M, Hraiech S, Demory D, Allardet-Servent J, Adda M, Barreau-Baumstark K, Castanier M, Papazian L, Roch A. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2012;40:1539–1545.
17. Gu X-L, Wu G-N, Yao Y-W, Shi D-H, Song Y. Is high-frequency oscillatory ventilation more effective and safer than conventional protective ventilation in adult acute respiratory distress syndrome patients? A meta-analysis of randomized controlled trials. *Crit Care* 2014;18:R111.
18. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
19. Adhikari NKJ, Bashir A, Lamontagne F, Mehta S, Ferguson ND, Zhou Q, Hand L, Czarnecka K, Cook DJ, Granton JT, *et al*. High-frequency oscillation in adults: a utilization review. *Crit Care Med* 2011;39: 2631–2644.