The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2013 VOL. 368 NO. 9

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

Previous trials suggesting that high-frequency oscillatory ventilation (HFOV) reduced mortality among adults with the acute respiratory distress syndrome (ARDS) were limited by the use of outdated comparator ventilation strategies and small sample sizes.

METHODS

In a multicenter, randomized, controlled trial conducted at 39 intensive care units in five countries, we randomly assigned adults with new-onset, moderate-to-severe ARDS to HFOV targeting lung recruitment or to a control ventilation strategy targeting lung recruitment with the use of low tidal volumes and high positive end-expiratory pressure. The primary outcome was the rate of in-hospital death from any cause.

RESULTS

On the recommendation of the data monitoring committee, we stopped the trial after 548 of a planned 1200 patients had undergone randomization. The two study groups were well matched at baseline. The HFOV group underwent HFOV for a median of 3 days (interquartile range, 2 to 8); in addition, 34 of 273 patients (12%) in the control group received HFOV for refractory hypoxemia. In-hospital mortality was 47% in the HFOV group, as compared with 35% in the control group (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; P=0.005). This finding was independent of baseline abnormalities in oxygenation or respiratory compliance. Patients in the HFOV group received higher doses of midazolam than did patients in the control group (199 mg per day [interquartile range, 100 to 382] vs. 141 mg per day [interquartile range, 68 to 240], P<0.001), and more patients in the HFOV group than in the control group received neuromuscular blockers (83% vs. 68%, P<0.001). In addition, more patients in the HFOV group received vasoactive drugs (91% vs. 84%, P=0.01) and received them for a longer period than did patients in the control group (5 days vs. 3 days, P=0.01).

CONCLUSIONS

In adults with moderate-to-severe ARDS, early application of HFOV, as compared with a ventilation strategy of low tidal volume and high positive end-expiratory pressure, does not reduce, and may increase, in-hospital mortality. (Funded by the Canadian Institutes of Health Research; Current Controlled Trials numbers, ISRCTN42992782 and ISRCTN87124254, and ClinicalTrials.gov numbers, NCT00474656 and NCT01506401.)

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This article was published on January 22, 2013, at NEJM.org.

N Engl J Med 2013;368:795-805.
DOI: 10.1056/NEJMoa1215554

The acute respiratory distress syndrome (ARDS) is a common complication of critical illness.[1,2] Mortality is high, and survivors often have long-term complications.[3,4] Although mechanical ventilation is life-sustaining for patients with ARDS, it can perpetuate lung injury. Basic research suggests that repetitive overstretching or collapse of lung units with each respiratory cycle can generate local and systemic inflammation, contributing to multiorgan failure and death.[5] Consistent with these findings are data from clinical trials that support the use of smaller tidal volumes (6 vs. 12 ml per kilogram of predicted body weight)[6] and higher levels of positive end-expiratory pressure (PEEP).[7-10] Mortality remains high, however, and additional therapies are needed to protect the lung in cases of severe ARDS.[11,12]

One such approach is high-frequency oscillatory ventilation (HFOV), which delivers very small tidal volumes (approximately 1 to 2 ml per kilogram[13]) at very high rates (3 to 15 breaths per second).[14-19] Previous randomized trials of the use of HFOV in adults with ARDS have suggested that this strategy results in improvements in oxygenation and survival, but the trials were limited by small sample sizes and outdated ventilation strategies for the control group.[20-22] Consequently, despite the frequent use of HFOV in patients who do not have an adequate response to conventional mechanical ventilation and the increased use of HFOV earlier in the course of the disease, this approach remains an unproven therapy for adults with ARDS.[23-26] We therefore compared HFOV with a conventional ventilation strategy that used low tidal volumes and high levels of PEEP in patients with new-onset, moderate-to-severe ARDS.

Methods

Study Oversight

For the pilot phase of the study, we enrolled patients at 11 centers in Canada and 1 in Saudi Arabia from July 2007 through June 2008; for the main trial, we enrolled patients at the same centers and at an additional 27 centers in Canada, the United States, Saudi Arabia, Chile, and India from July 2009 through August 2012 (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol, which is available at NEJM.org, was approved by the research ethics board at each participating site. The first and last author vouch for the accuracy and completeness of the reported data and for the fidelity of this report to the study protocol. For HFOV, we used the SensorMedics 3100B High-Frequency Oscillatory Ventilator (CareFusion); the manufacturer loaned nine ventilators and provided technical support but had no role in the design of the study, the collection or analysis of the data, or the preparation of the manuscript.

Patients

Patients were eligible for inclusion if they had had an onset of pulmonary symptoms within the previous 2 weeks, had undergone tracheal intubation, had hypoxemia (defined as a ratio of the partial pressure of arterial oxygen [Pao_2] to the fraction of inspired oxygen [Fio_2] of ≤200, with an Fio_2 of ≥0.5), and had bilateral air-space opacities on chest radiography. Patients were excluded if they had hypoxemia primarily related to left atrial hypertension, suspected vasculitic pulmonary hemorrhage, neuromuscular disorders that are known to prolong the need for mechanical ventilation, severe chronic respiratory disease, or preexisting conditions with an expected 6-month mortality exceeding 50%; if they were at risk for intracranial hypertension; if there was a lack of commitment to life support; if the expected duration of mechanical ventilation was less than 48 hours; if they were younger than 16 years of age or older than 85 years of age; or if their weight was less than 35 kg or more than 1 kg per centimeter of height. We did not enroll patients who had already met the eligibility criteria for more than 72 hours, those who were already receiving HFOV, or those whose physicians declined to enroll them.

After enrollment, standardized ventilator settings were used for all the patients: pressure-control mode, a tidal volume of 6 ml per kilogram, and an Fio_2 of 0.60 with a PEEP level of 10 cm of water or higher if needed for oxygenation. After 30 minutes, if the Pao_2:Fio_2 ratio remained at 200 or lower, patients underwent randomization; otherwise the standardized ventilator settings were maintained, and the patients were reassessed at least once daily for up to 72 hours. Eligible patients were randomly assigned in a 1:1 ratio to the HFOV group or to the conventional-ventilation group. Randomization was performed in undisclosed block sizes of 2 and 4 with the use of a central Web-based

Table 1. Ventilator Protocols.*

Component Variable	HFOV	Control Ventilation
Ventilator mode	High-frequency oscillatory ventilation	Pressure control
Tidal volume target (ml/kg of predicted body weight)	NA	6
Tidal volume range (ml/kg of predicted body weight)	NA	4–8
Plateau airway pressure (cm of water)	NA	≤35
Positive end-expiratory pressure (cm of water)	NA	Adjusted according to oxygenation†
Mean airway pressure (cm of water)	Adjusted according to oxygenation†	Measured but not adjusted
Respiratory frequency	3–12 Hz	≤35 breaths/min
Pressure amplitude target (cm of water)	90	NA
Partial pressure of arterial oxygen (mm Hg)	55–80	55–80
Oxygen saturation by pulse oximetry (%)	88–93	88–93
Arterial blood pH	7.25–7.35	7.30–7.45
Ratio of inspiratory-to-expiratory time	1:2	1:1–1:3
Recruitment maneuvers	Yes	Yes

* The full version of the study protocol is available at NEJM.org. HFOV denotes high-frequency oscillatory ventilation, and NA not applicable.
† For more information on the protocol for adjustment, see Table 2.

randomization system, stratified according to center. All patients or their legal surrogates provided written informed consent for participation in the study.

HFOV PROTOCOL

The HFOV protocol was designed on the basis of the results of pilot testing and consensus guidelines.[24,27] We first conducted a recruitment maneuver, by applying 40 cm of water pressure for 40 seconds to the airway opening in an effort to reopen closed lung units. We then initiated HFOV with a mean airway pressure of 30 cm of water, adjusting the pressure thereafter according to the protocol, targeting a Pao_2 of 55 to 80 mm Hg (Tables 1 and 2). We minimized HFOV tidal volumes by using the highest possible frequency that would maintain arterial blood pH above 7.25.[13,28]

After 24 hours of HFOV, conventional ventilation could be resumed if the mean airway pressure was 24 cm of water or less for 12 hours. This transition was mandatory when airway pressures reached 20 cm of water. Thereafter, mechanical ventilation followed the control protocol. Over the next 48 hours, if an F_{IO_2} of more than 0.4 or a PEEP level of more than 14 cm of water was required for more than 1 hour to achieve oxygenation targets, HFOV was resumed.

Table 2. Usual Combinations of the Fraction of Inspired Oxygen (F_{IO_2}) and Positive End-Expiratory Pressure (PEEP) or Mean Airway Pressure Used to Adjust Ventilators.

HFOV		Control Ventilation	
F_{IO_2}	Mean Airway Pressure	F_{IO_2}	PEEP
	cm of water		*cm of water*
0.4	20	0.3	5
0.4	22	0.3	8
0.4	24	0.3	10
0.4	26	0.4	10
0.4	28	0.4	12
0.4	30	0.4	14
0.5	30	0.4	16
0.6	30	0.4	18
0.6	32	0.5	18
0.6	34	0.5	20
0.7	34	0.6	20
0.8	34	0.7	20
0.9	34	0.8	20
1.0	34	0.8	22
1.0	36	0.9	22
1.0	38	1.0	22
		1.0	24

CONTROL VENTILATION PROTOCOL

The control ventilation protocol, which was adapted from an earlier trial,[9] called for a target tidal volume of 6 ml per kilogram, with plateau airway pressure of 35 cm of water or less and high levels of PEEP. After an initial recruitment maneuver (the same as that used for the HFOV group), clinicians applied ventilation using pressure-control mode with a PEEP level of 20 cm of water and then adjusted the PEEP level and the F_{IO_2} according to the protocol (Tables 1 and 2). The protocol permitted the use of volume-assist control mode or pressure-support mode with the same limits for tidal volumes and airway pressures. For patients receiving pressure support with PEEP levels of 10 cm of water or less and an F_{IO_2} of 0.4 or less, there were no limits on tidal volume or airway pressures. The weaning protocol, which has been published previously, included daily trials of spontaneous breathing.[9,29]

PROCEDURES IN BOTH GROUPS

When hypoxemia persisted despite increases in PEEP or mean airway pressure, or when, on the basis of radiographic or clinical evidence, physicians judged that the lungs were over-distended, they could reduce PEEP or mean airway pressure to a level below that indicated in the assigned protocol (Table 2).

For patients with hypoxemia who required an F_{IO_2} of 0.9 or greater, clinicians could institute therapies for hypoxemia (e.g., prone positioning or inhaled nitric oxide) that did not interfere with the assigned ventilator protocols. Physicians could institute any alternative therapy (including HFOV in the control group) for patients who met any one of the following criteria: refractory hypoxemia (P_{AO_2} <60 mm Hg for 1 hour with an F_{IO_2} of 1.0 and neuromuscular blockade), refractory barotrauma (persistent pneumothorax or increasing subcutaneous emphysema despite two thoracostomy tubes on the involved side), or refractory acidosis (pH of ≤7.05 despite neuromuscular blockade).

Physicians prescribed fluids, sedatives, and neuromuscular blockers at their discretion. We recorded cardiorespiratory variables daily as well as data on cointerventions applied while patients were undergoing mechanical ventilation for up to 60 days. Intensivists reviewed chest radiographs for evidence of new barotrauma. Patients were followed until their discharge from the hospital.

STATISTICAL ANALYSIS

We anticipated that mortality in the control group would be 45%. Assuming a two-sided alpha level of 0.05, we calculated that enrollment of 1200 patients would provide at least 80% power to detect a relative-risk reduction with HFOV of 20%, even if mortality in the control group was as low as 37%.

Investigators reviewed feasibility data from the pilot phase, which involved 94 patients, but remained unaware of the clinical outcomes. The independent data monitoring committee reviewed the clinical outcomes from the pilot phase and recommended that the trial continue to the next phase. As originally planned, data from the patients involved in the pilot phase were included in the current analyses. In addition to an interim analysis after 800 patients had undergone randomization, safety analyses of physiological data at the initiation of the study were planned after 300, 500, and 700 patients had undergone randomization. After reviewing these safety data, the data monitoring committee could request analyses of in-hospital mortality, which they did after both the 300-patient and 500-patient safety analyses. With plans to stop the study early only in response to a strong signal of harm in association with the use of HFOV, we used the O'Brien–Fleming method to calculate alpha spending and generated one-sided P values for considering early stopping after random assignment of 300 patients ($P \leq 0.00001$), 500 patients ($P \leq 0.0001$), and 700 patients ($P \leq 0.0064$).

We used SAS software, version 9.2, for the statistical analyses. We summarized data using means with standard deviations, medians and interquartile ranges, or proportions. Normally distributed data were compared with the use of Student's t-test, nonnormally distributed data with the use of the Wilcoxon rank-sum test, and proportions with the use of the Mantel–Haenszel chi-square test, with stratification according to center. We analyzed data from all patients according to their assigned group.

The primary outcome was in-hospital mortality, with the outcome compared between the two groups stratified according to center. Other than recording whether death occurred as a result of withdrawal of life support, we did not record specific causes of death. As a sensitivity analysis, we used logistic regression to adjust the treatment effect for prespecified baseline vari-

ables: age, the Acute Physiology Score component of the Acute Physiology and Chronic Health Evaluation (APACHE) II score,[30] the presence or absence of sepsis, and the duration of hospitalization before randomization.[9] To compare the two groups with respect to the time to death, we used a survival analysis, in which patients who were discharged alive from the hospital were assumed to be alive at day 60.

We conducted prespecified subgroup analyses to determine whether there were interactions of the treatment effect with baseline severity of lung injury (in quartiles of the Pao_2:Fio_2 ratio) or with center experience with HFOV and study protocols (in thirds of number of patients recruited). In addition, we studied interactions of the treatment effect with baseline dynamic compliance measured from tidal breaths during conventional ventilation (in quartiles), baseline body-mass index (in quartiles), and receipt or no receipt of vasopressors at baseline — all post hoc analyses.

RESULTS

EARLY TERMINATION OF THE TRIAL

After the 500-patient analysis, the steering committee terminated the trial, acting on a unanimous recommendation from the data monitoring committee, although the threshold P value for stopping had not been reached. At the time of termination, 571 patients had been enrolled, of whom 548 had undergone randomization: 275 to the HFOV group and 273 to the control-ventilation group (Fig. 1). Important prognostic factors were similar in the two groups at baseline (Table 3, and Table S1 in the Supplementary Appendix).

MORTALITY

A total of 129 patients (47%) in the HFOV group, as compared with 96 patients (35%) in the control group, died in the hospital (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; P=0.005) (Table 4 and Fig. 2). The results were consistent in a multivariable analysis (Table S2 in the Supplementary Appendix), in an analysis of mortality in the intensive care unit (ICU), and in an analysis of 28-day mortality. Subgroup analyses showed no interaction of mortality with baseline severity of hypoxemia, respiratory compliance, body-mass index, or use or nonuse of vasopressors or with center experience in the trial (Fig. S1 in the Supplementary Appendix).

EARLY PHYSIOLOGICAL RESPONSES TO VENTILATION

Table S3 in the Supplementary Appendix shows early physiological responses to HFOV and to control ventilation. The use of vasopressors was similar in the HFOV and control groups before the initiation of ventilation (66% and 61%, respectively; P=0.24) but increased in the HFOV group as compared with the control group within 4 hours after initiation (73% vs. 62%, P=0.01) and increased even more in the HFOV group by the following day (78% vs. 58%, P<0.001). The use of neuromuscular blockers followed a similar pattern: 27% of patients in the HFOV group and 29% of those in the control group received neuromuscular blockers before the initiation of ventilation (P=0.66), 46% as compared with 31% received them within 4 hours after initiation (P<0.001), and 46% as compared with 26% received them the next day (P<0.001). The mean Fio_2 at these time points decreased to a similar extent in both groups: the Fio_2 was 0.75 in the HFOV group and 0.73 in the control group before initiation (P=0.93); 0.62 and 0.64 in the two groups, respectively, 4 hours after initiation (P=0.94); and 0.51 and 0.50, respectively, the next day (P=0.97).

CARDIORESPIRATORY RESULTS

Table S4 in the Supplementary Appendix shows cardiorespiratory data from the first week of the study. On day 1, the mean (±SD) of the mean airway pressure in the HFOV group was 31±2.6 cm of water, with a frequency of 5.5±1.0 Hz; patients in the control group underwent ventilation with a tidal volume of 6.1±1.3 ml per kilogram, PEEP of 18±3.2, and plateau pressure of 32±5.7 cm of water. The mean Fio_2 in the control group was similar to or lower than that in the HFOV group, despite lower mean airway pressures. The net fluid balance was higher in the HFOV group than in the control group, but the difference was not significant. In the HFOV group, 270 of the 275 patients (98%) underwent HFOV for a median of 3 days (interquartile range, 2 to 8); a total of 222 patients (81%) survived and were transitioned to conventional ventilation for a further 5 days (interquartile range, 2 to 7). In the control group, 34 patients (12%) crossed over to HFOV (31 according to protocol and 3 in violation of protocol) for 7 days (interquartile range, 5 to 15), beginning 2 days (interquartile range, 1 to 4) after randomization; 24 of those 34 patients (71%) died in the hospital.

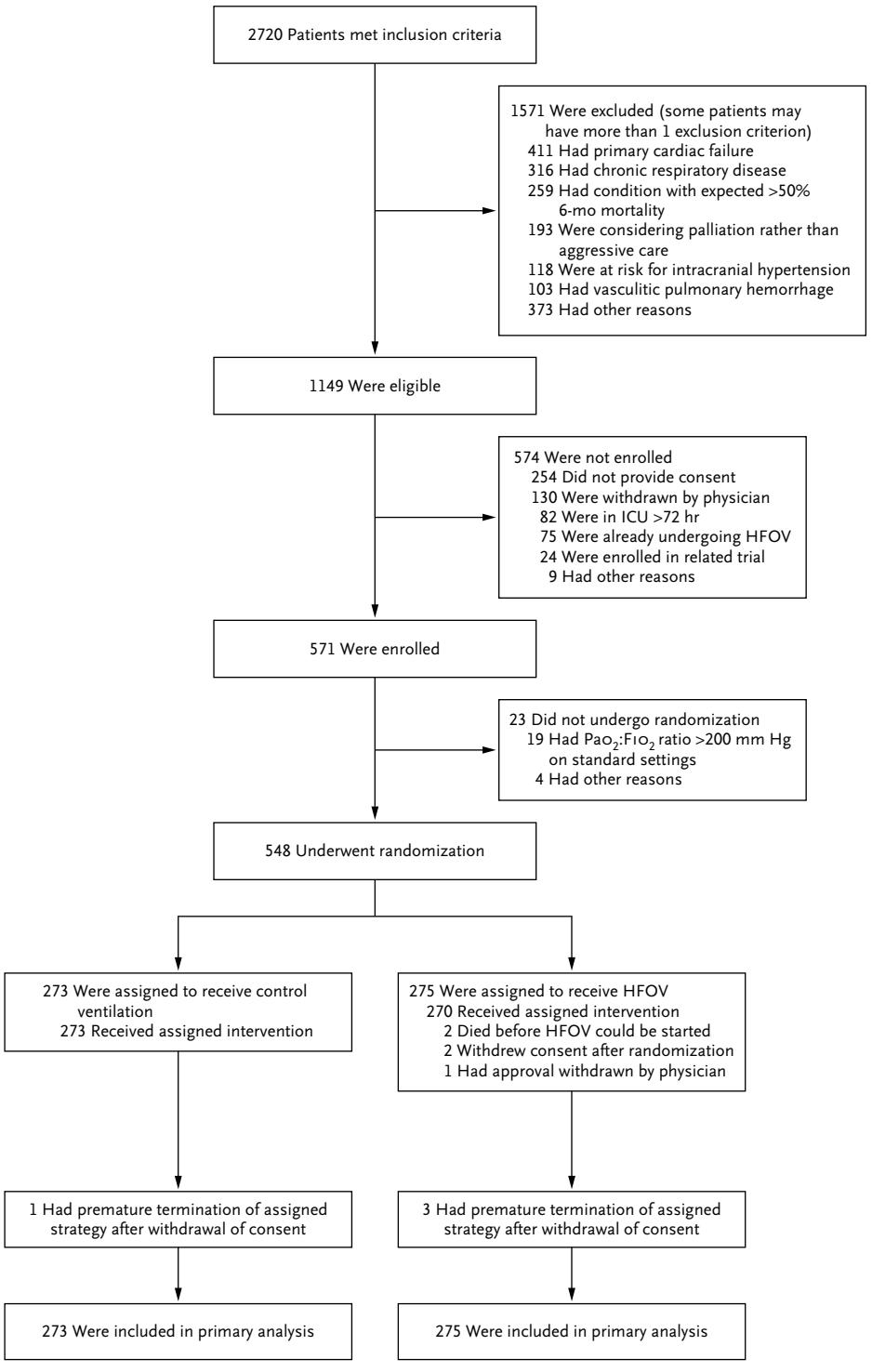

Figure 1. Screening, Randomization, and Follow-up.

HFOV denotes high-frequency oscillatory ventilation, ICU intensive care unit, and Pao_2:FIO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

Table 3. Baseline Characteristics of the Patients.*

Characteristic	HFOV Group (N=275)	Control Group (N=273)	Patients Eligible but Not Enrolled (N=472)†	P Value‡
Age — yr	55±16	54±16	53±16	0.18
Female sex — no. (%)	108 (39)	120 (44)	198 (42)	0.42
APACHE II score§	29±8	29±7	26±8	<0.001
Duration of hospital stay — days	5.6±8.0	4.9±8.0		
Duration of mechanical ventilation — days	2.5±3.3	1.9±2.3		
Risk factors for ARDS — no. of patients (%)				
Sepsis	128 (47)	130 (48)	193 (41)	0.01
Pneumonia	155 (56)	164 (60)	289 (61)	0.37
Gastric aspiration	49 (18)	44 (16)	51 (11)	0.02
Trauma	10 (4)	5 (2)	24 (5)	0.07
Other	71 (26)	67 (25)	137 (29)	0.34
Tidal volume — ml/kg of predicted body weight	7.2±1.9	7.1±1.8		
Plateau pressure — cm of water	29±6	29±7	27±7	<0.001
Set PEEP — cm of water	13±3	13±4	11±4	<0.001
Minute ventilation — liters/min	11.3±3.1	11.2±3.3		
Oxygenation index	19.6±11.2	19.9±9.3	17.8±10.2	0.002
Pao_2:FIo_2 ratio — mm Hg	121±46	114±38	118±47	0.17
$Paco_2$ — mm Hg	46±13	47±14	45±14	0.01
Arterial pH	7.32±0.10	7.31±0.10	7.32±0.12	0.06
Barotrauma — no. of patients (%)	19 (7)	14 (5)		
Cointerventions — no. of patients (%)				
Inotropes or vasopressors	184 (67)	171 (63)		
Renal-replacement therapy	29 (11)	28 (10)		
Glucocorticoids	93 (34)	96 (35)		
Neuromuscular blockers	84 (31)	94 (34)		

* Plus–minus values are means ±SD. There were no significant differences between the two study groups in any of the baseline characteristics listed here, with the exception of duration of mechanical ventilation, for which P=0.003. ARDS denotes acute respiratory distress syndrome, and Pao_2 partial pressure of arterial oxygen.

† Not all centers had approval from an ethics committee to collect data on patients who were eligible but not enrolled in the study.

‡ The P values are for the comparison of patients who were eligible but not enrolled with all patients who underwent randomization, with adjustment for stratification according to center.

§ Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating greater severity of illness.

COINTERVENTIONS

During the course of the study, larger proportions of patients in the HFOV group than in the control group received vasoactive drugs (91% vs. 84%, P=0.01) and neuromuscular blockers (83% vs. 68%, P<0.001); vasoactive drugs were administered for an average of 2 days longer in the HFOV group than in the control group, and neuromuscular blockers were administered for an average of 1 day longer in the HFOV group (Table S5 in the Supplementary Appendix). Sedatives and opioids (most commonly midazolam and fentanyl) were administered for the same duration in the two groups (median, 10 days [interquartile range, 6 to 18] and 10 days [interquartile range, 6 to 17], respectively; P=0.99), but during the first week the

Table 4. Outcomes.

Outcome	HFOV Group (N = 275)	Control Group (N = 273)	Relative Risk (95% CI)	P Value
Death in hospital — no. (%)	129 (47)	96 (35)	1.33 (1.09–1.64)	0.005
Death in intensive care unit — no. (%)	123 (45)	84 (31)	1.45 (1.17–1.81)	0.001
Death before day 28 — no. (%)	111 (40)	78 (29)	1.41 (1.12–1.79)	0.004
New barotrauma — no./total no. (%)*	46/256 (18)	34/259 (13)	1.37 (0.91–2.06)	0.13
New tracheostomy — no./total no. (%)†	59/273 (22)	66/267 (25)	0.87 (0.64–1.19)	0.39
Refractory hypoxemia — no. (%)	19 (7)	38 (14)	0.50 (0.29–0.84)	0.007
Death after refractory hypoxemia — no./total no. (%)	15/19 (79)	25/38 (66)	1.20 (0.87–1.66)	0.31
Refractory acidosis — no. (%)	9 (3)	8 (3)	1.12 (0.44–2.85)	0.82
Refractory barotrauma — no. (%)	2 (<1)	2 (<1)	0.99 (0.14–7.00)	0.99
Use of mechanical ventilation, among survivors — days				0.59
Median	11	10		
Interquartile range	7–19	6–18		
Stay in intensive care, among survivors — days				0.93
Median	15	14		
Interquartile range	9–25	9–26		
Length of hospitalization, among survivors — days				0.74
Median	30	25		
Interquartile range	16–45	15–41		

* Barotrauma was defined as pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema occurring spontaneously or after a recruitment maneuver. Excluded from this category were patients who had barotrauma at baseline.

† Excluded from this category were patients who had a tracheostomy at baseline.

median doses of midazolam were significantly higher in the HFOV group than in the control group (199 mg per day [interquartile range, 100 to 382] vs. 141 mg per day [interquartile range, 68 to 240], P<0.001), and there was a trend toward higher doses of fentanyl equivalents in the HFOV group (2980 μg per day [interquartile range, 1258 to 4800] vs. 2400 μg per day [interquartile range, 1140 to 4430], P=0.06) (for daily doses of selected sedative and analgesic drugs, see Fig. S2 in the Supplementary Appendix). The rates of use of other cointerventions, including glucocorticoids, renal-replacement therapy, and prone positioning, were similar in the two groups (Table S5 in the Supplementary Appendix).

OTHER OUTCOMES

Refractory hypoxemia developed in significantly more patients in the control group than in the HFOV group; however, the total number of deaths after refractory hypoxemia was similar in the two groups (Table 4). The proportion of deaths after withdrawal of life support was similar in the two groups (55% [71 of 129 patients] in the HFOV group and 49% [47 of 96 patients] in the control group, P=0.12). The rate of new-onset barotrauma was higher in the HFOV group than in the control group, but the difference was not significant (18% and 13%, respectively; P=0.13). Among survivors, the duration of ventilation and the length of stay in the ICU were similar in the two groups (Table 4).

DISCUSSION

The main finding of this multicenter, randomized trial is that among patients with moderate-to-severe ARDS, early application of HFOV was associated with higher mortality than was a ventilation strategy that used small tidal volumes and high PEEP levels, with HFOV used only in patients with severe refractory hypoxemia. HFOV

was associated with higher mean airway pressures and with greater use of sedatives, neuromuscular blockers, and vasoactive drugs.

We stopped the trial early on the basis of a strong signal for increased mortality with HFOV, even though the prespecified stopping thresholds had not been reached. Studies that are stopped early on the basis of harm (or benefit) typically overestimate the magnitude of effect.[31] We chose to terminate the study for three reasons: there was a consistent finding of increased mortality with HFOV in three consecutive analyses that were conducted after enrollment of 94, 300, and 500 patients; the increased need for vasoactive drugs in the HFOV group suggested a mechanism of harm that was not offset by better oxygenation and lung recruitment; and the effect size was sufficiently large that we concluded that even if early HFOV did not increase mortality, it would be very unlikely to decrease mortality. We believe that continued enrollment would have put patients at risk with little likelihood of benefit.

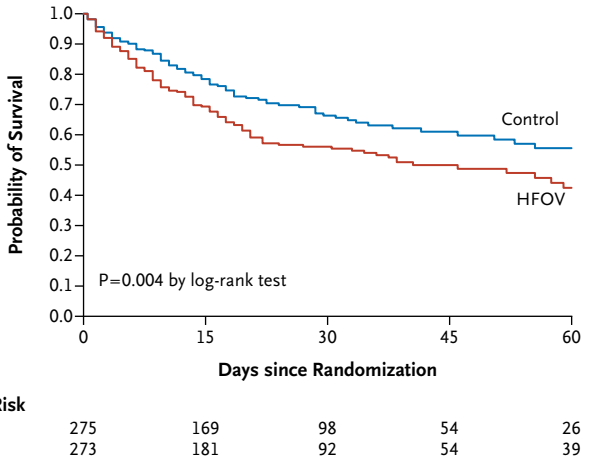

Figure 2. Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.

Our results are inconsistent with the physiological rationale for HFOV and with the results of studies in animals. In studies in animals in which benefits of HFOV were observed, lung injury was induced with the use of saline lavage — a highly recruitable model of surfactant deficiency — which our results suggest does not translate directly to human adults with ARDS, in whom recruitability can be heterogeneous.[32] Our results also contrast with those of prior randomized trials involving adults.[22] A possible explanation, which provided motivation for our trial, is that prior studies used control ventilation strategies that are now known to be potentially harmful.[20,21] We found no benefit with HFOV when a current ventilation strategy was used as a control. This finding of no benefit with respect to mortality is consistent with the results of another trial now reported in the *Journal*; in that trial, conducted in the United Kingdom, current standards for lung protection were suggested but not mandated.[33] More surprising was our finding of harm. Several plausible mechanisms may contribute to increased mortality with HFOV. Higher mean airway pressures may result in hemodynamic compromise by decreasing venous return or directly affecting right ventricular function.[34] Increased use of vasodilating sedative agents may also contribute to hemodynamic compromise. Moreover, we cannot exclude the possibility of increased barotrauma in association with HFOV.

The HFOV strategy that we chose, which was supported by preclinical data[15,16] and a prospective physiological study,[24] aimed to adjust mean airway pressure on the deflation limb of the volume-pressure curve and use the highest frequency possible to limit oscillatory volumes. This approach led to relatively high mean airway pressures, even considering that when mean airway pressures are delivered with a ratio of inspiratory-to-expiratory time of 1:2, as in our study, the pressures measured at the airway opening during HFOV are somewhat higher than those measured in the trachea.[35-37] It is possible that an HFOV protocol that uses lower mean airway pressures, a different ratio of inspiratory-to-expiratory time, or a lower oscillatory frequency might have led to different results.

The strengths of this trial include its methodologic rigor, the application of protocols designed to open lung units in patients in both groups on the basis of the best available evidence, and enrollment at centers in several countries, which enhances the generalizability of our findings. Because we were cognizant that there is a learning curve associated with the use of HFOV,[38,39] we enrolled most patients at centers that were experienced with HFOV, and we did not detect an interaction between treatment effect and the number of enrolled patients per site.

Our results raise serious concerns about the early use of HFOV for the management of ARDS in adults. The results of this study increase the uncertainty about possible benefits of HFOV even when applied in patients with life-threatening refractory hypoxemia.

In conclusion, in adults with moderate-to-severe ARDS, the early application of HFOV targeting lung recruitment — as compared with a ventilation strategy that uses low tidal volume and high PEEP and that permits HFOV only in cases of refractory hypoxemia — does not reduce mortality and may be harmful.

Supported by the Canadian Institutes of Health Research, Randomized Controlled Trial (RCT) Program (Ottawa) and the King Abdullah International Medical Research Center (Riyadh, Saudi Arabia). Dr. Ferguson is supported by a Canadian Institutes of Health Research New Investigator Award; Dr. Cook holds a Canada Research Chair; Dr. Lamontagne is supported by a Fonds de Recherche de Québec–Santé Research Career Award; and Drs. Ferguson and Meade and Drs. Lamontagne and Meade were supported by Canadian Institutes of Health Research RCT Mentorship awards.

Dr. Ferguson reports receiving grant support through his institution from the Physicians Services Incorporated Foundation; Dr. Granton, receiving consulting fees from Ikaria, lecture fees from Actelion and Eli Lilly, grant support through his institution from Pfizer, Actelion, Eli Lilly, GlaxoSmithKline, and Bayer, payment through his institution from Telus for the sale of a software site license, and support from Actelion for his hospital foundation for pulmonary hypertension research and providing expert testimony for Pfizer regarding patent legal action; and Dr. Slutsky, receiving consulting fees from Maquet Medical, Novalung, Gambro, Ikaria, and Hemodec. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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