EDITORIAL

High-Frequency Oscillatory Ventilation on Shaky Ground

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We thought it was impossible. Physiological principles maintained that ventilation at tidal volumes less than the anatomical deadspace should be ineffective (i.e., inspired air not reaching the alveolae). Data from a 1980 study dispelled that myth, showing unequivocally that ventilation with tidal volumes as small as 20 to 30 ml in dogs, a mere fraction of the anatomical deadspace, could maintain adequate ventilation.[1] These unexplained observations sparked transport and mixing theories predicting that CO_2 removal should vary in direct proportion to breathing frequency (although the relationship with tidal volume is more complex[2,3]), and these predictions were later confirmed experimentally.[4] Subsequent studies showed that CO_2 removal eventually reaches a plateau when the airways narrow during expiration, indicating the onset of expiratory-flow limitation. This concept is important, since portions of the lung can become hyperinflated dynamically (i.e., regional air trapping) beyond levels predicted from the applied mean airway pressure.[5-7]

High-frequency oscillatory ventilation (HFOV), in which small tidal volumes are applied at a high respiratory rate, became a focus of research and clinical practice, but widespread use was limited by the unavailability of commercial equipment. As the technology gradually evolved, the field suffered setbacks when trials showed that HFOV did not provide a benefit and could have induced harm in neonates with the respiratory distress syndrome.[8,9] Although there have been some small clinical trials,[10] the use of HFOV in adult patients never really caught on. More and better data were needed, and the field evolved as our understanding of the physiology of the acute respiratory distress syndrome (ARDS) improved.

Although mechanical ventilation can clearly be life-sustaining for those who are critically ill, there are now compelling data showing that mechanical ventilation can be damaging to the lung if the ventilator is set inappropriately. Excessive tidal volumes can stretch the lung, leading to overdistention and further lung injury.[11] Inadequate positive end-expiratory pressure (PEEP) can promote repetitive alveolar collapse followed by reopening, which may be injurious to the lung (an injury known as atelectrauma). Lung homogeneity is also thought to be important, since injurious forces can develop at junctions of normal and abnormal lung even when the applied pressures are modest.[12] Thus, in theory, HFOV in a well-recruited, homogeneous lung could avoid these problems if the problems with local airflow velocity could be overcome. If so, HFOV could combine small pressure oscillations to minimize overdistention with high mean airway pressures to prevent atelectrauma (Fig. 1).

Two major, multicenter, randomized trials now reported in the *Journal* show that it is hard to put theory into practice. In the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial,[14] the authors found that an HFOV strategy with high mean airway pressures led to more deaths than did a conventional mechanical-ventilation strategy that used relatively high PEEP levels. Patients in both groups underwent a baseline recruitment maneuver (sustained high-pressure inflation) to promote lung homogeneity. 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), a finding that led to premature termination of the trial. The mechanism underlying the poor HFOV outcomes appears to

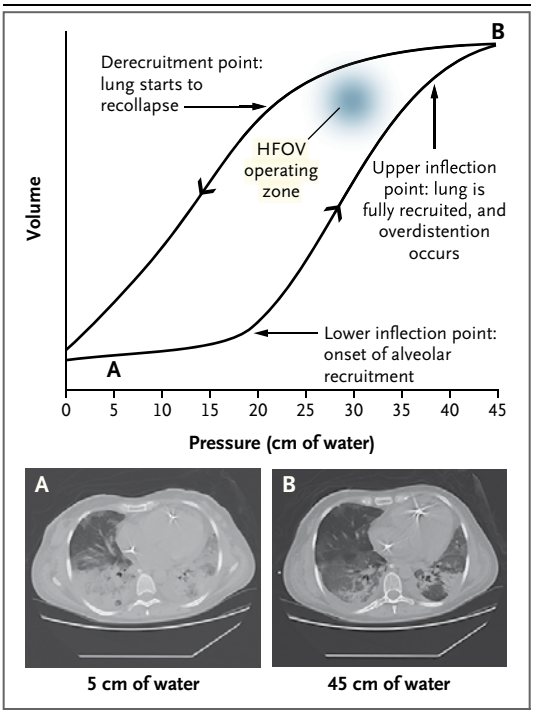

Figure 1. Schematic Diagram of a Pressure-Volume Curve of a Lung in a Patient with the Acute Respiratory Distress Syndrome.

The inflation limb (lower curve) and deflation limb (upper curve) differ from one another. The lower inflection point defines the onset of alveolar recruitment from a state of substantial collapse; the lung below this point is illustrated in the axial computed tomographic (CT) scan in Panel A. The upper inflection point is thought to reflect the point at which recruitment is no longer occurring and overdistention may start to occur; the lung in this condition is illustrated in the axial CT scan in Panel B. High-frequency oscillatory ventilation (HFOV) is performed on the deflation limb of the pressure-volume curve; in this form of ventilation, small volumes should help to limit overdistention, and high mean airway pressures should prevent injury from repetitive collapse and reopening of the lung. CT scans adapted from Gattinoni et al.[13] The CT scans in Panels A and B correspond to the areas marked A and B in the upper panel.

have been hemodynamic compromise, since the elevated mean airway pressures with HFOV were associated with increased requirements for pressor medications and probably end-organ failures. Was the disconnect between mean airway pressure and regional lung volume noted above at play here?

In the Oscillation in ARDS (OSCAR) trial,[15] the authors found no major difference in the outcome between an HFOV strategy and usual care with conventional mechanical ventilation. The rate of death from any cause at 28 days was 41.7% in the HFOV group and 41.1% in the usual-care control group (P=0.85 by the chi-square test). The hemodynamic compromise associated with HFOV that was induced by high mean airway pressures was minimal in the OSCAR trial as compared with the OSCILLATE trial, perhaps owing to lower applied ventilatory pressures in the OSCAR trial. In accordance with the pragmatic design of the OSCAR trial, there was considerable variance in the management of the disease in the usual-care control group in that trial, perhaps reflecting physician judgment and therapy that was individualized to patient characteristics.[16] In both the OSCAR and OSCILLATE trials, the patients in the HFOV groups received more sedatives and muscle relaxants than did the patients in the control groups, which perhaps also contributed to the disappointing outcomes. Thus, both trials are helpful in raising caution about widespread routine clinical use of HFOV.

What are the conclusions? First, these data might suggest that HFOV, as applied in these trials, is not an advance. However, one could argue that it is not HFOV itself but the HFOV protocols studied in these trials that were ineffective, and perhaps worse, than usual care. Whether the reduction in preload induced by high mean airway pressures in the OSCILLATE trial could have been mitigated by more aggressive volume resuscitation,[7] without worsening lung edema, is unclear. Similarly, whether further elevation in mean airway pressures applied to a well-recruited lung may have improved lung protection in the OSCAR trial is also unclear. If iatrogenic injury from heavy sedation or paralysis could be minimized while the comfort of the patient is maintained, perhaps the theoretical benefits of HFOV would be realized.

Second, patient selection may be an important factor. Some patients have recruitable lung (i.e., lung tissue in which alveolar air volume is increased with small increases in airway pressure), whereas others have nonrecruitable lung. Among patients with homogeneous, recruitable lung, increasing mean airway pressure may well be beneficial; however, among patients with heterogeneous and nonrecruitable lung, increasing mean airway pressure may lead to overdistention of some lung regions without increased aeration of collapsed or flooded alveoli. Such in-

dexes of recruitability (which can be assessed, perhaps, with the use of regional imaging or measures of lung or chest-wall mechanics) may help to define which patients may benefit from high mean airway pressures and which patients are likely to suffer deleterious effects without major lung protection. For example, applied ventilatory pressures can affect pleural pressure, which in turn influences hemodynamics, but the interactions are complicated and are dependent on relative lung and chest-wall compliance, left and right ventricular function, volume status, and other factors.

Third, currently recommended strategies that use low tidal volumes may have effectively minimized mechanical stress on the lung,[17] and further improvements in outcomes are likely to occur only through improved understanding of the heterogeneous ARDS phenotype and its underlying biologic characteristics. Perhaps patients with ARDS will require individualized therapy that takes into consideration their body habitus, the cause of their disease, and the mechanisms leading to lung injury. Considerable discussion will ensue about which patients should be included and which technologies should be used in the next trial, but for now clinicians should be cautious about applying HFOV routinely in patients with ARDS.

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

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1. Bohn DJ, Miyasaka K, Marchak BE, et al. Ventilation by high-frequency oscillation. J Appl Physiol 1980;48:710-6.
2. Fredberg JJ. Augmented diffusion in the airways can support pulmonary gas exchange. J Appl Physiol 1980;49:232-8.
3. Weinmann GG, Mitzner W, Permutt S. Physiological dead space during high-frequency ventilation in dogs. J Appl Physiol 1984;57:881-7.
4. Slutsky AS, Drazen JM, Ingram RH Jr, et al. Effective pulmonary ventilation with small-volume oscillations at high frequency. Science 1980;209:609-71.
5. Rossing TH, Slutsky AS, Lehr JL, Drinker PA, Kamm R, Drazen JM. Tidal volume and frequency dependence of carbon dioxide elimination by high-frequency ventilation. N Engl J Med 1981;305:1375-9.
6. Venegas JG, Fredberg JJ. Understanding the pressure cost of ventilation: why does high-frequency ventilation work? Crit Care Med 1994;22:Suppl:S49-S57.
7. Kolton M, Cattran CB, Kent G, et al. Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. Anesth Analg 1982;61:323-32.
8. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.
9. Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002;347:633-42.
10. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166:801-8.
11. The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volume for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301-8.
12. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970;28:596-608.
13. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
14. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215554.
15. Young D, Lamb S, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215716.
16. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-104.
17. Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med 2007;357:1113-20.

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ORIGINAL ARTICLE

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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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 Fio_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 (Fio_2) and Positive End-Expiratory Pressure (PEEP) or Mean Airway Pressure Used to Adjust Ventilators.

HFOV		Control Ventilation	
Fio_2	Mean Airway Pressure	Fio_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 (Pa_{O_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.

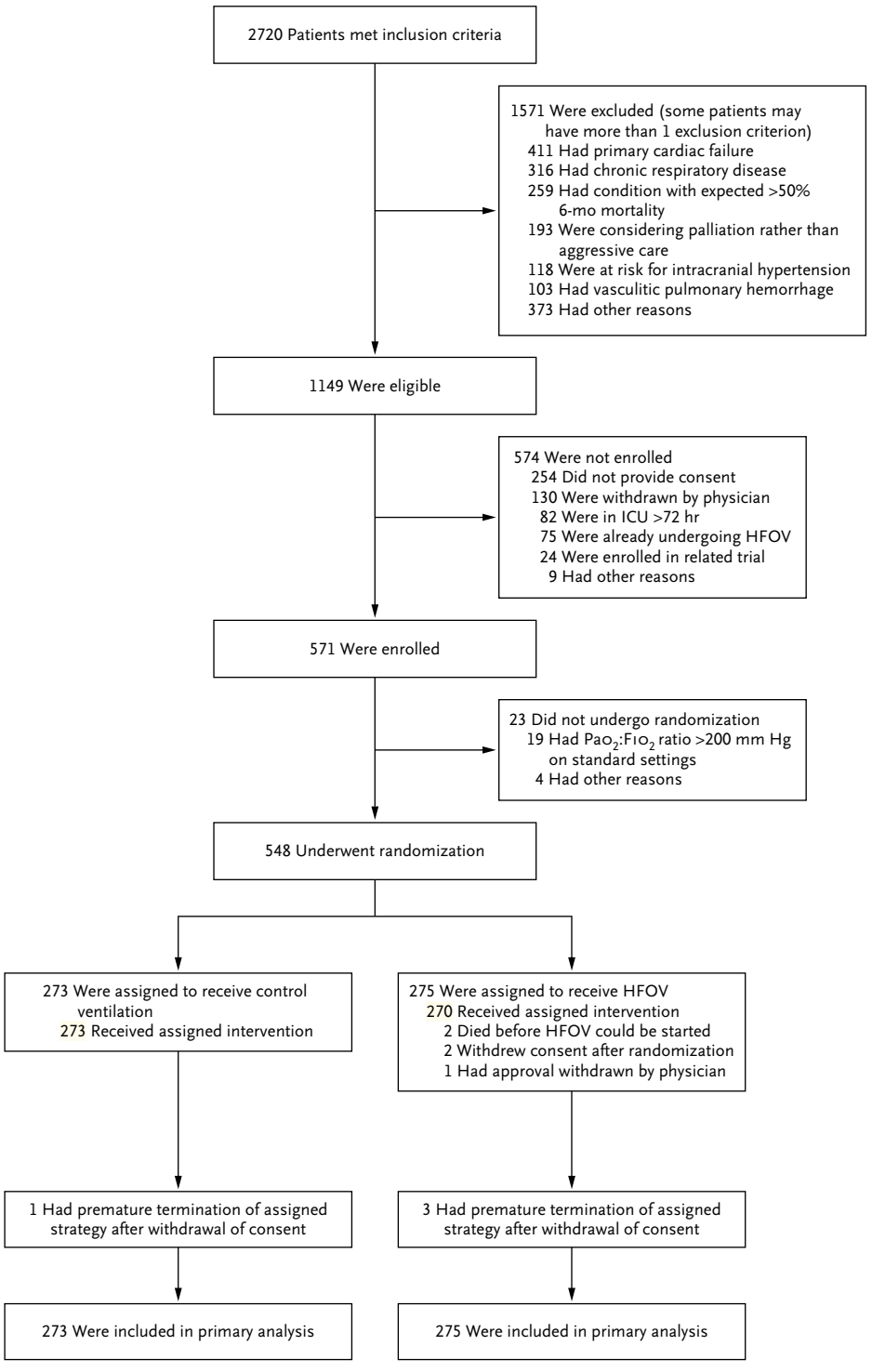

Figure 1. Screening, Randomization, and Follow-up.

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
Pao_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.

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.

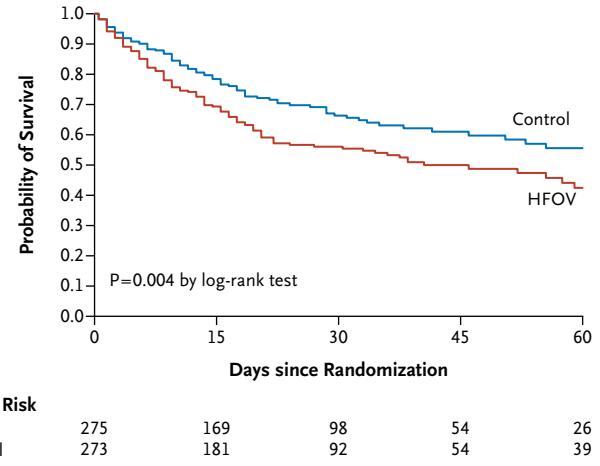

Figure 2. Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.

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.

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

REFERENCES

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
2. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685-93.
3. Phua J, Badia JR, Adhikari NKJ, et al. Has mortality from acute respiratory distress syndrome decreased over time? Am J Respir Crit Care Med 2009;179:220-7.
4. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293-304.
5. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006;32:24-33.
6. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
7. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327-36.
8. Mercat A, Richard J-CM, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646-55.
9. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:637-45.
10. Briel M, Meade M, Mercat A, 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;303:865-73.
11. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;175:160-6.
12. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology 2009;111:826-35.
13. Hager DN, Fessler HE, Kaczka DW, et al. Tidal volume delivery during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2007;35:1522-9.
14. Ferguson ND, Slutsky AS, Kacmarek R. High-frequency ventilation is/is not the optimal physiological approach to ventilate ARDS patients. J Appl Physiol 2008;104:1230-1.
15. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time. Crit Care Med 1997;25:906-8.
16. Rimensberger PC, Pache JC, McKerlie C, Frndova H, Cox PN. Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation. Intensive Care Med 2000;26:745-55.
17. Imai Y, Nakagawa S, Ito Y, Kawano T, Slutsky AS, Miyasaka K. Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. J Appl Physiol 2001;91:1836-44.
18. Muellenbach RM, Kredel M, Said HM, et al. High-frequency oscillatory ventilation reduces lung inflammation: a large-animal 24-h model of respiratory distress. Intensive Care Med 2007;33:1423-33.
19. Sedeek KA, Takeuchi M, Suchodolski K, et al. Open-lung protective ventilation with pressure control ventilation, high-frequency oscillation, and intratracheal pulmonary ventilation results in similar gas exchange, hemodynamics, and lung mechanics. Anesthesiology 2003;99:1102-11.
20. Derdak S, Mehta S, Stewart TE, et al. High frequency oscillatory ventilation for acute respiratory distress syndrome: a randomized controlled trial. Am J Respir Crit Care Med 2002;166:801-8.
21. Bollen CW, van Well GT, Sherry T, et al. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial. Crit Care 2005;9:R430-R439.
22. Sud S, Sud M, Friedrich JO, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. BMJ 2010;340:c2327.
23. Fort P, Farmer C, Westerman J, et al. High-frequency oscillatory ventilation for adult respiratory distress syndrome — a pilot study. Crit Care Med 1997;25:937-47.
24. Ferguson ND, Chiche J-D, Kacmarek RM, et al. Combining high-frequency oscillatory ventilation and recruitment maneuvers in adults with early acute respiratory distress syndrome: the Treatment with Oscillation and an Open Lung Strategy (TOOLS) Trial pilot study. Crit Care Med 2005;33:479-86.
25. Mehta S, Granton J, MacDonald RJ, et al. High-frequency oscillatory ventilation

in adults: the Toronto experience. Chest 2004;126:518-27.
26. Adhikari NKJ, Bashir A, Lamontagne F, et al. High-frequency oscillation in adults: a utilization review. Crit Care Med 2011;39:2631-44.
27. Fessler HE, Derdak S, Ferguson ND, et al. A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. Crit Care Med 2007;35:1649-54.
28. Fessler HE, Hager DN, Brower RG. Feasibility of very high-frequency ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2008;36:1043-8.
29. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 1995;332:345-50.
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
31. Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-9.
32. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
33. Young D, Lamb S, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215716.
34. Guervilly C, Forel J-M, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2012;40:1539-45.
35. Hatcher D, Watanabe H, Ashbury T, Vincent S, Fisher J, Froese A. Mechanical performance of clinically available, neonatal, high-frequency, oscillatory-type ventilators. Crit Care Med 1998;26:1081-8.
36. Pillow JJ, Neil H, Wilkinson MH, Ramsden CA. Effect of I/E ratio on mean alveolar pressure during high-frequency oscillatory ventilation. J Appl Physiol 1999;87:407-14.
37. Mentzelopoulos SD, Malachias S, Kokkoris S, Roussos C, Zakynthinos SG. Comparison of high-frequency oscillation and tracheal gas insufflation versus standard high-frequency oscillation at two levels of tracheal pressure. Intensive Care Med 2010;36:810-6.
38. The HiFi Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.
39. Bryan AC, Froese AB. Reflections on the HIFI trial. Pediatrics 1991;87:565-7.

ORIGINAL ARTICLE

High-Frequency Oscillation for Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

Patients with the acute respiratory distress syndrome (ARDS) require mechanical ventilation to maintain arterial oxygenation, but this treatment may produce secondary lung injury. High-frequency oscillatory ventilation (HFOV) may reduce this secondary damage.

METHODS

In a multicenter study, we randomly assigned adults requiring mechanical ventilation for ARDS to undergo either HFOV with a Novalung R100 ventilator (Metran) or usual ventilatory care. All the patients had a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of 200 mm Hg (26.7 kPa) or less and an expected duration of ventilation of at least 2 days. The primary outcome was all-cause mortality 30 days after randomization.

RESULTS

There was no significant between-group difference in the primary outcome, which occurred in 166 of 398 patients (41.7%) in the HFOV group and 163 of 397 patients (41.1%) in the conventional-ventilation group (P=0.85 by the chi-square test). After adjustment for study center, sex, score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, and the initial PaO_2:FIO_2 ratio, the odds ratio for survival in the conventional-ventilation group was 1.03 (95% confidence interval, 0.75 to 1.40; P=0.87 by logistic regression).

CONCLUSIONS

The use of HFOV had no significant effect on 30-day mortality in patients undergoing mechanical ventilation for ARDS. (Funded by the National Institute for Health Research Health Technology Assessment Programme; OSCAR Current Controlled Trials number, ISRCTN10416500.)

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The acute respiratory distress syndrome (ARDS) is a severe, diffuse inflammatory lung condition caused by a range of acute illnesses. Mortality in affected patients is high,[1] and survivors may have functional limitations for years.[2,3] Although mechanical ventilation can initially be lifesaving in patients with ARDS, it can also further injure the patients' lungs and contribute to death.[4]

High-frequency oscillatory ventilation (HFOV) was first used experimentally in the 1970s to minimize the hemodynamic effects of mechanical ventilation.[5] Patients' lungs are held inflated to maintain oxygenation, and carbon dioxide is cleared by small volumes of gas moved in and out of the respiratory system at 3 to 15 Hz. This action is thought to minimize the repeated process of opening and collapsing of lung units that causes the secondary lung damage during mechanical ventilation. On the basis of small trials with outdated controls[6] and the commercial availability of HFOV equipment, many clinicians use HFOV for patients who have hypoxemia despite the use of standard approaches for improving arterial oxygenation. The increasing use of HFOV in the absence of good evidence of effectiveness led the National Institute for Health Research in the United Kingdom to commission a study to determine the effectiveness of HFOV as a treatment for ARDS.

Methods

Study Design

We conducted a randomized, controlled trial of HFOV, as compared with conventional mechanical ventilation. Patients were recruited from adult general intensive care units (ICUs) in 12 university hospitals, 4 university-affiliated hospitals, and 13 district general hospitals in England, Wales, and Scotland. Three hospitals had previous experience with HFOV with the use of SensorMedics 3100B ventilators (CareFusion), and the remainder had limited experience (in 6 hospitals) or no experience (in 20 hospitals) with HFOV. Details regarding HFOV training are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The full protocol is also available at NEJM.org.

The ventilators were purchased from Inspiration Healthcare. The company had no role in the study design, data acquisition, data analysis, or manuscript preparation. The study was approved by national ethics review committees and research governance departments at each center. Patients or their representatives provided written informed consent.

Patients

Patients who were undergoing mechanical ventilation were eligible for the study if they had a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of 200 mm Hg (26.7 kPa) or less while receiving a positive end-expiratory pressure (PEEP) of 5 cm of water or greater, if bilateral pulmonary infiltrates were visible on chest radiography without evidence of left atrial hypertension, and if they were expected to require at least 2 more days of mechanical ventilation.

Patients were excluded if they had undergone mechanical ventilation for 7 or more days, if they were under the age of 16 years, if they weighed less than 35 kg, if they were participating in other interventional studies, if they had lung disease characterized by airway narrowing or air trapping, or if they had undergone recent lung surgery.

An independent telephone randomization system assigned patients to either HFOV or conventional mechanical ventilation in a 1:1 ratio. Randomization was by permuted block stratified according to study center, PaO_2:FIO_2 ratio (≤113 mm Hg [15 kPa] or >113 mm Hg), age (≤55 years or >55 years), and sex. Each center had one HFOV ventilator, so recruitment could not take place if the device was in use for another study patient.

Study Treatments

Patients in the HFOV group were treated with the use of a Novalung R100 ventilator (Metran)[7] until the start of weaning. The initial settings were a ventilation frequency of 10 Hz, a mean airway pressure of 5 cm of water above the plateau airway pressure at enrollment, bias flow rate of 20 liters per minute, a cycle volume of 100 ml (the volume of gas used to move the oscillating diaphragm; the tidal volume delivered to the alveoli is a fraction of this volume), and an inspired oxygen fraction of 1. This ventilator has a fixed 1:1 inspiratory:expiratory time ratio.

Two algorithms were used to determine changes in HFOV settings (for details, see the Supple-

mentary Appendix). The partial pressure of arterial carbon dioxide ($PaCO_2$) was controlled to maintain an arterial pH above 7.25 by increasing the cycle volume to the maximum at each frequency. If this was insufficient, the frequency was reduced by 1 Hz. If the minimum frequency (5 Hz) was reached, the on-call study clinician would suggest other measures to control the $PaCO_2$ level (see the Supplementary Appendix).

The PaO_2 level was maintained between 60 mm Hg and 75 mm Hg (8 kPa to 10 kPa). Hypoxemia was treated by increasing the mean airway pressure and then by increasing the FIO_2 level. If a patient reached a mean airway pressure of 24 cm of water, at an FIO_2 level of 0.4 or less, with a PaO_2 level of 60 mm Hg or greater, for 12 hours or more, he or she was switched to pressure-controlled ventilation for weaning from mechanical ventilation, since there was no facility to accommodate patients' spontaneous respiratory efforts during HFOV. Patients could be restarted on HFOV up to 2 days after the start of weaning.

Patients in the conventional-ventilation group were treated according to local practice in the participating ICUs. The participating units were encouraged to use pressure-controlled ventilation at 6 to 8 ml per kilogram of ideal body weight and to use the combinations of PEEP and FIO_2 values that were used in the Acute Respiratory Distress Syndrome Network study.[4] All other treatment was determined by the patients' physicians on the basis of assessment of clinical need.

DATA COLLECTION

At the time of enrollment, we recorded data with respect to the patients' demographic characteristics, ventilation before enrollment, physiology and other data required to calculate the score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, coexisting medical conditions, the use of sedatives and muscle relaxants, and ventilator settings. For each day that a patient was treated in the ICU, we recorded data with respect to the use of antibiotics, sedatives, and muscle relaxants during the previous day or since enrollment on the first day. Data regarding support for respiratory and cardiovascular organ systems were recorded daily during treatment in the ICU with the use of the United Kingdom's critical-care minimum data set.[8] Vital status at 30 days was known for all patients, but causes of death were not recorded.

OUTCOMES

The primary outcome, vital status at 30 days, was obtained from hospital records and verified with the use of a national database. Secondary outcomes were all-cause mortality at the time of discharge from the ICU and the hospital, the duration of mechanical ventilation, and the use of antimicrobial, sedative, vasoactive, and neuromuscular-blocking drugs. We recorded the duration of treatment in both the ICU and the hospital.

STATISTICAL ANALYSIS

Recruitment-rate estimates and sample-size calculations were performed after a systematic review of the incidence and outcome of ARDS, national audits in the United Kingdom, and two randomized, controlled trials of HFOV.[9,10] We determined that the enrollment of 503 patients per study group would provide a power of 80% to identify a change of 9 percentage points in an estimated rate of death of 45% in the control group at a P value of 0.05. At a planned interim review, the sample size was revised to 401 patients per group on the basis of accumulated mortality data in the control group and an effect size of 10 percentage points (80% power at $P=0.05$).

All analyses were conducted on an intention-to-treat basis. Three planned interim analyses were conducted by an independent data and safety monitoring committee after the recruitment of 100, 340, and 640 patients. Formal stopping rules were not specified. Instead, the committee assessed whether the randomized comparisons provided "proof beyond reasonable doubt" that for all or some patients the treatment was clearly indicated or clearly contraindicated and provided evidence that might reasonably be expected to influence future patient treatment.

We used chi-square tests to compare between-group rates of death at 30 days and among patients in ICU and hospital settings. We performed an analysis of mortality after adjustment for study center, sex, PaO_2:FIO_2 ratio, and APACHE II score using logistic regression. Continuous variables were compared with the use of Student's t-tests. Since both the rate and timing of death were similar in the two study groups, data for survivors and those for nonsurvivors were not analyzed separately. All P values are two-sided.

RESULTS

TRIAL PROGRESSION AND RECRUITMENT

We trained 2306 intensive care nurses, medical staff, physiotherapists, and technicians in 198 face-to-face training sessions. Patients were recruited from December 7, 2007, until the end of July 2012. Of the 2769 patients who were screened, 795 (28.7%) underwent randomization (Fig. 1). The study had 968 ICU-months of recruitment averaging 0.82 patients per ICU-month. (A graphical summary of recruitment is provided in Figure S3 in the Supplementary Appendix.) The baseline characteristics of the patients at randomization were similar in the two study groups (Table 1).

VENTILATION

HFOV was used for a median of 3 days (interquartile range, 2 to 5) in 388 patients. The longest initial period of receipt of HFOV was 24 days. Figure 2 shows the use of HFOV in the two study groups. Ten patients in the conventional-ventilation group underwent HFOV at some point during the study period, and 10 patients who were assigned to the HFOV group never received this treatment. Table 2 shows ventilatory and other variables for the first 3 days of the study period.

Neuromuscular-blocking drugs were used for a mean (±SD) of 2.0±3.4 days in the conventional-ventilation group and for 2.5±3.5 days in the HFOV group (P=0.02). Sedative drugs were used for 8.5±6.9 days in the conventional-ventilation group and for 9.4±7.2 days in the HFOV group (P=0.07).

The patients had 17.6±8.8 ventilator-free days in the conventional-ventilation group and 17.1±8.6 ventilator-free days in the HFOV group (P=0.42). Mechanical ventilation (including HFOV but excluding noninvasive ventilation) was used for 14.1±13.4 days in the conventional-ventilation group and 14.9±13.3 days in the HFOV group (P=0.41).

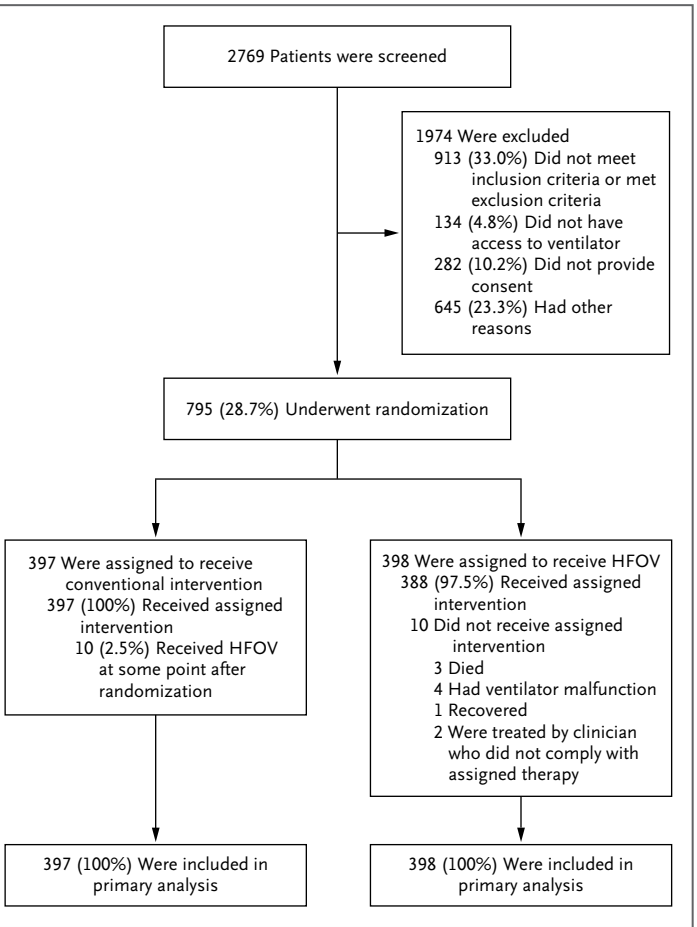

Figure 1. Enrollment and Outcomes.
HFOV denotes high-frequency oscillatory ventilation.

OUTCOMES

The primary outcome occurred in 166 of 398 patients (41.7%) in the HFOV group and in 163 of 397 patients (41.1%) in the conventional-ventilation group (P=0.85), for an absolute difference of 0.6 percentage points (95% confidence interval [CI], −6.1 to 7.5). After adjustment for study center, sex, APACHE II score, and Pa_{O_2}:F_{IO_2} ratio, the odds ratio for survival in the conventional-ventilation group, as compared with the HFOV group, was 1.03 (95% CI, 0.75 to 1.40; P=0.87 by logistic regression) (Fig. 3). Similar proportions of patients died at each time point in each group.

The rates of death at first discharge from the ICU were 42.1% in the conventional-ventilation group and 44.1% in the HFOV group, for an absolute difference of 2.0 percentage points (P=0.57). At first hospital discharge, 48.4% of patients in the conventional-ventilation group and 50.1% of those in the HFOV group had died, for an absolute difference of 1.7 percentage points (P=0.62).

Data are not provided with respect to the duration of care for survivors and nonsurvivors, since the proportions of patients who died in each study group over time were nearly identical. The total duration of ICU stay was 16.1±15.2 days in the conventional-ventilation group and 17.6±16.6 days in the HFOV group (P=0.18); the total durations of hospital stay were 33.1±44.3 days and

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Conventional Ventilation (N=397)	HFOV (N=398)	All Patients (N=795)
Age — yr	55.9±16.2	54.9±18.8	55.4±16.2
Male sex — no. (%)	239 (60.2)	256 (64.3)	495 (62.3)
APACHE II score†	21.7±6.1	21.8±6.0	21.8±6.1
Probability of in-hospital death (as calculated from APACHE II score)	0.43±0.19	0.44±0.19	0.43±0.19
Pa_{O_2}:F_{IO_2} ratio — mm Hg	113±38	113±37	113±38
Exhaled tidal volume — ml	505±173	541±271	523±228
Exhaled tidal volume — ml/kg of ideal body weight‡	8.3±3.5	8.7±3.5	8.5±3.9
Exhaled minute ventilation — liters/min	10.17±3.46	10.41±3.25	10.29±3.35
Positive end-expiratory pressure — cm of water	11.3±3.3	11.4±3.5	11.4±3.4
Duration of mechanical ventilation before randomization — days	2.1±2.1	2.2±2.3	2.2±2.2
Pulmonary cause of ARDS — no. (%)	304 (76.6)	302 (75.9)	606 (76.2)

* Plus–minus values are means ±SD. There was no significant difference between groups except for exhaled tidal volume (P=0.04). ARDS denotes acute respiratory distress syndrome, F_{IO_2} fraction of inspired oxygen, and Pa_{O_2} partial pressure of arterial oxygen.
† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II scale range from 0 to 71, with higher scores indicating more severe disease.[11]
‡ Ideal body weight was calculated as 2.3 kg for each inch of height above 60 in. added to 50 kg for men or 45.5 kg for women.

33.9±41.6 days, respectively (P=0.79). As of October 1, 2012, the date that the database was closed, 7 patients remained in acute hospital care.

Patients received antimicrobial drugs for 12.4±10.3 days in the conventional-ventilation group and for 12.8±12.0 days in the HFOV group (P=0.56); 67.5% and 64.4% of these drugs, respectively, were administered to treat pulmonary infections.

There was no significant difference in the number of days on which patients received inotropic agents or pressor infusions, with 2.8±5.6 days in the conventional-ventilation group and 2.9±4.5 days in the HFOV group (P=0.74).

DISCUSSION

This study, which was designed to help practitioners choose between options for care, met 7 of the 10 criteria of the Pragmatic–Explanatory Continuum Indicator Summary (PRECIS).[12] The results were not totally pragmatic because of the tight protocol-specified restrictions on the use of HFOV, protocol-compliance monitoring, and additional follow-up. We found no significant between-group difference in the primary outcome of mortality up to 30 days after randomization. Our estimate of the 95% confidence interval for the treatment excludes the treatment effect we specified in both the initial and revised sample-size estimates. Since data collection is ongoing, we cannot yet report the longer-term outcomes (including survival and health-related quality of life).

We recruited patients with moderate-to-severe ARDS, with an average Pa_{O_2}:F_{IO_2} ratio of 113 mm Hg (15.1 kPa). The study-entry criterion was a Pa_{O_2}:F_{IO_2} ratio of less than 200 mm Hg (26.7 kPa), which was in line with the agreed definition of ARDS,[13] but the additional requirement of a further 48 hours or more of mechanical ventilation may have excluded milder cases of ARDS. The average Pa_{O_2}:F_{IO_2} ratio is nearly identical to the mean of 112 mm Hg reported in the recent systematic review of HFOV[6] and is similar to the mean values reported in studies of other treatments for ARDS.[14-16] The patients had a high severity of illness, as evidenced by the APACHE II scores, which also were nearly identical to those reported in the two other multicenter studies of HFOV in adults.[9,10] Thus, we appear to have recruited patients who were similar to those in previous randomized, controlled trials of HFOV.

HFOV improved oxygenation as expected. The

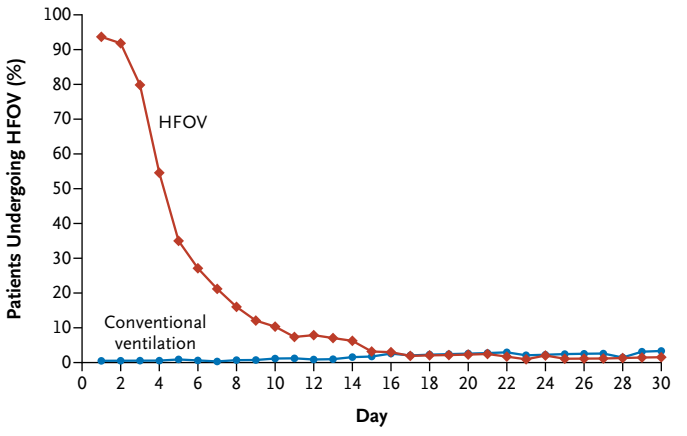

Figure 2. Proportions of Patients Undergoing High-Frequency Oscillatory Ventilation (HFOV) during the First 30 Days, According to Study Group.

Shown are the percentages of patients in each study group who underwent HFOV. Ten patients in the conventional-ventilation group underwent HFOV at some point during their treatment, and 10 patients who were assigned to the HFOV group never received this treatment. Day 0 is the day of randomization, and subsequent determinations were made at 8 a.m. each day.

$Paco_2$ value increased as a predicted result of the HFOV treatment algorithms, resulting in a modest respiratory acidosis. A similar effect was seen in the larger of the two reported studies of HFOV in adults[10] but not in the smaller study[9] or the meta-analysis.[6] The conventional-ventilation group was treated with tidal volumes at the upper end of the accepted range of 6 to 8 ml per kilogram of ideal body weight.

The use of HFOV was initially associated with an increased use of neuromuscular-blocking drugs, probably because the R100 ventilator has no facility to allow the patient to breathe spontaneously. HFOV has been reported to cause a reduction in cardiac output,[17] but as indicated by the use of vasoactive and inotropic drugs, that did not occur in this study.

Our results are at variance with the latest meta-analysis of HFOV,[6] which showed a reduced risk of death (risk ratio, 0.77; 95% CI, 0.61 to 0.98), as compared with conventional ventilation. This may be simply that our study recruited more than twice the number of patients who were included

Table 2. Ventilatory Variables during the First 3 Study Days.*

Variable	Day 1		Day 2		Day 3	
	HFOV	Conventional Ventilation	HFOV	Conventional Ventilation	HFOV	Conventional Ventilation
No. of patients	370	392	326	374	240	348
Mean airway pressure (HFOV) or plateau pressure (conventional ventilation) — cm of water	26.9±6.2	30.9±11.0	25.3±5.5	29.5±10.7	25.1±5.4	28.5±11.2
Total respiratory frequency — Hz (HFOV) or breaths/min (conventional ventilation)	7.8±1.8	21.7±8.4	7.5±1.8	22.7±9.0	7.2±1.8	23.3±8.2
Cycle volume (HFOV) or tidal volume (conventional ventilation) — ml (HFOV) or ml/kg of ideal body weight (conventional ventilation)	213±72	8.3±2.9	228±75	8.2±2.5	240±75	8.3±3.0
Positive end-expiratory pressure — cm of water (conventional ventilation only)	NA	11.4±3.6	NA	11.0±3.6	NA	10.5±3.7
Pao_2:Fio_2 ratio — mm Hg	192±77	154±61	212±69	163±66	217±69	166±63
$Paco_2$ — mm Hg	55±17	50±19	56±16	49±13	56±17	48±13
Arterial pH	7.30±0.10	7.35±0.10	7.32±0.09	7.37±0.10	7.34±0.10	7.39±0.09
Medication use — no. (%)†						
Neuromuscular-blocking agent	209 (52.5)	165 (41.6)	147 (36.9)	115 (29.0)	110 (27.6)	77 (19.4)
Vasoactive or inotropic agent	173 (43.5)	177 (44.6)	158 (40.0)	146 (36.8)	126 (31.7)	112 (28.2)
Sedative agent	390 (98.0)	388 (97.7)	371 (93.2)	363 (91.4)	341 (85.7)	335 (84.4)

* Measurements were taken at 8 a.m. Day 1 values were recorded the morning after recruitment. The values for high-frequency oscillatory ventilation (HFOV) are only for patients who actually underwent the treatment. The values for conventional ventilation are for all patients assigned to receive conventional ventilation who were receiving any mechanical ventilation. NA denotes not applicable, and $Paco_2$ partial pressure of arterial carbon dioxide.

† Percentages were calculated on the basis of the 398 patients in the HFOV group and the 397 patients in the conventional-ventilation group who underwent randomization.

in the meta-analysis. Adding our results to the meta-analysis changes the estimated risk ratio from the pooled studies to 0.90 (95% CI, 0.76 to 1.07), indicating no significant benefit for HFOV.

The use of HFOV is a lung-protection strategy, which may be ineffective if it is used for too brief a period. We used it up to the point at which the HFOV design hindered weaning. In the two other multicenter studies of HFOV in adults,[9,10] the duration of ventilation was not reported.

In the HFOV group in our study, we used the Novalung R100 ventilator, a device that had not been used before in clinical trials. To date, all studies have used the SensorMedics 3100B ventilator, a device that has an electromechanically driven diaphragm, which normally oscillates with an inspiratory:expiratory time ratio of 1:2. The R100 ventilator uses a pneumatically driven diaphragm with a fixed 1:1 ratio. It seems unlikely that these differences would explain the difference in mortality between our study and the pooled results of studies to date, but it remains a possibility.

We recruited patients who met the definition of ARDS[13] that was in place at the time the study was planned, and the entry criteria match the "moderate" and "severe" categories in the recently revised definition.[18] The study has good internal and external validity. Bias was minimized by using centers with equipoise, by concealing treatment assignments before randomization, by concealing interim analyses from all study investigators except for the data and safety monitoring committee, and by using an analysis plan that was agreed on before study closure. There was no loss to follow-up, crossovers were minimal, and the study recruited 99.1% of the planned sample size. External validity was maintained by using a large number of different-sized ICUs spread across the United Kingdom. Most of the centers in this trial were inexperienced with the intervention at the start, but this was unavoidable, since few centers in the United Kingdom have experience with the use of HFOV. We invested heavily in training at each study center. The consent-refusal rate was low.

Our report coincides with the publication in the *Journal* of the results of a large multicenter efficacy study of HFOV, the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial.[19] This study showed 47% mortality in the HFOV group and 35% in the control group. The patients who were recruited in both studies were broadly similar. The OSCILLATE trial used the 3100B ventilator, maneuvers to reexpand collapsed areas of lung before HFOV, and a protocol-specified high-PEEP strategy for conventional ventilation. In that study, the patients undergoing HFOV required more inotropic and pressor support than did those in the control group. It is possible that the HFOV strategy used in the OSCILLATE trial was injurious, but the low mortality in their control group also raises the possibility that the control treatment was a very effective ventilation strategy in patients with ARDS.

In conclusion, in a large effectiveness study, we were unable to find any benefit or harm from the use of HFOV in adult patients with ARDS. We recommend that this mode of ventilation not be used for routine care.

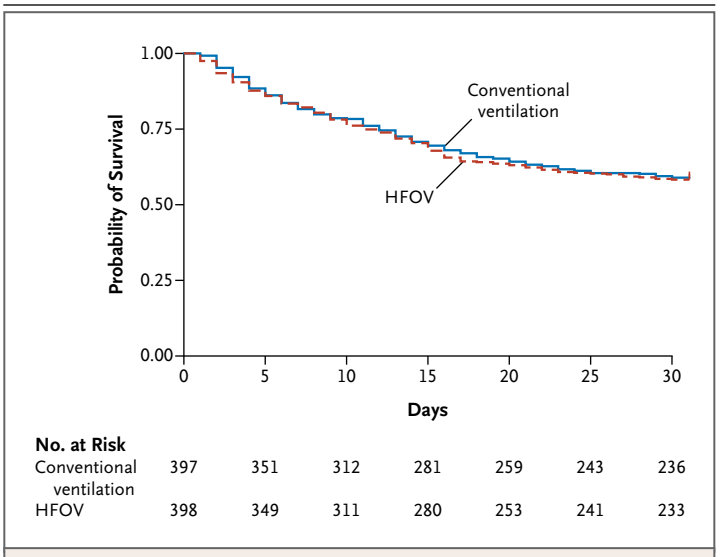

Figure 3. Kaplan–Meier Survival Estimates during the First 30 Study Days.

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

REFERENCES

1. Erickson SE, Martin GS, Davis JL, Matthay MA, Eisner MD. Recent trends in acute lung injury mortality: 1996-2005. Crit Care Med 2009;37:1574-9.

2. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293-304.

3. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683-93.

4. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
5. Lunkenheimer PP, Rafflenbeul W, Keller H, Frank I, Dickhut HH, Fuhrmann C. Application of transtracheal pressure oscillations as a modification of "diffusing respiration." Br J Anaesth 1972;44:627.
6. Sud S, Sud M, Friedrich JO, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. BMJ 2010;340:c2327.
7. Metran. Product information: R100. 2012 (http://www.metran.co.jp/en/product/r100/index.html).
8. Critical care minimum dataset, version 8.0, revised March 2010 (http://www.isb.nhs.uk/documents/isb-0153/amd-81-2010/0153812010spec.pdf).
9. Bollen CW, van Well GT, Sherry T, et al. High frequency oscillation ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. Crit Care 2005;9:R430-R439.
10. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166:801-8.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
12. Thorpe KE, Zwarenstein M, Oxman AD, et al. A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS): a tool to help trial designers. CMAJ 2009;180:E47-E57.
13. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
14. Villar J, Pérez-Méndez L, Basaldúa S, et al. A risk tertiles model for predicting mortality in patients with acute respiratory distress syndrome: age, plateau pressure, and PaO_2/FIO_2 at ARDS onset can predict mortality. Respir Care 2011;56:420-8.
15. Villar J, Blanco J, Añón JM, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med 2011;37:1932-41. [Erratum, Intensive Care Med 2011;37:1942.]
16. Perkins GD, Gates S, Lamb SE, McCabe C, Young D, Gao F. Beta Agonist Lung Injury TrIal-2 (BALTI-2) trial protocol: a randomised, double-blind, placebo-controlled of intravenous infusion of salbutamol in the acute respiratory distress syndrome. Trials 2011;12:113.
17. Mehta S, Lapinsky SE, Hallett DC, et al. Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. Crit Care Med 2001;29:1360-9.
18. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-33.
19. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215554.

CORRESPONDENCE

High-Frequency Oscillation for ARDS

TO THE EDITOR: In their article on the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) study, Ferguson et al. (Feb. 28 issue)[1] report increased mortality in patients with the acute respiratory distress syndrome (ARDS) who underwent high-frequency oscillatory ventilation (HFOV), probably because of elevated mean airway pressures. High levels of airway pressure may reduce venous return by elevating right atrial pressure, increasing venous resistance, and creating vascular waterfall conditions in the vena cava.[2,3] High levels of airway pressure may also increase pulmonary vascular resistance and right ventricular afterload through passive compression of alveolar vessels.[4] During HFOV, the mean airway pressure is a setup measure but is a dependent variable during conventional mechanical ventilation. It is influenced by inspiratory, expiratory, and total cycle times, alveolar pressure, tidal volume, inspiratory resistance, and positive end-expiratory pressure (PEEP)[5] (Fig. 1). The data presented by Ferguson et al. suggest that we should consider control of the mean airway pressure for circulatory protection of patients with ARDS who are undergoing mechanical ventilation, just as we learned to limit plateau pressure for lung protection.

$$\text{mean airway pressure} = \frac{Ri \times Vt}{Tt} + \frac{\left[\int_0^{Ti} PA \times dt\right]}{Tt} + PEEP \times \frac{Te}{Tt}$$

Figure 1. Determinants of Mean Airway Pressure.
The mean airway pressure is influenced by the inspiratory time (Ti), expiratory time (Te), and total cycle time (Tt), along with the time integral of the function of alveolar pressure (PA) during inspiration (dt), tidal volume (Vt), inspiratory resistance (Ri), and positive end-expiratory pressure (PEEP).

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1. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368:795-805.
2. Pinsky MR. Cardiovascular issues in respiratory care. Chest 2005;128:Suppl:592S-597S.
3. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. J Appl Physiol 2000;88:926-32.
4. Guervilly C, Forel JM, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2012;40:1539-45.
5. Marini JJ, Ravenscraft SA. Mean airway pressure: physiologic determinants and clinical importance — Part 2: clinical implications. Crit Care Med 1992;20:1604-16.

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TO THE EDITOR: Ferguson et al. found that the use of HFOV for the treatment of early ARDS was associated with an absolute increase of 12 per-

THIS WEEK'S LETTERS

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centage points in the rate of death, as compared with conventional ventilation. We are concerned that systematic differences between the sedation strategies used in the two study groups may explain the findings, as we discussed regarding the study of neuromuscular blockers for early ARDS reported by Papazian et al.[1,2]

Perception of discomfort associated with HFOV may predispose physicians to prescribe higher doses of vasodilating sedatives and analgesics than with conventional ventilation (approximately 750 μg of fentanyl and 50 mg of midazolam more per day with HFOV), a finding that was associated with the administration of an additional liter of fluid over the first 3 days to maintain hemodynamic stability. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) trial, investigators found an absolute increase in mortality of 10 percentage points for each liter of fluid accumulated during the first 72 hours,[3] a finding that approximated the increase in mortality reported in the study by Ferguson et al.

Perhaps if the anesthetic prescription included ketamine (similar to that used in the group receiving neuromuscular blocking agents in the study by Papazian et al.[1]), the combination of the opiate-sparing and vasoconstricting effects of ketamine[4] would attenuate sedation-related fluid requirements, and the benefit of HFOV would be realized.

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1. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
2. Csanyi-Fritz YI, McDermid RC. Neuromuscular blockade for early severe acute respiratory distress syndrome: does sedation make the difference? Can J Anaesth 2012;59:503.
3. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344-53.
4. Hoka S, Takeshita A, Yamamoto K, Ito N, Yoshitake J. The effects of ketamine on venous capacitance in rats. Anesthesiology 1985;62:145-8.

DOI: 10.1056/NEJMc1304344

TO THE EDITOR: The OSCILLATE study and the Oscillation in ARDS (OSCAR)[1] trial by Young et al. have provided robust data on the outcome of HFOV among patients with ARDS. However, we wonder whether the key message — namely, the critical importance of lower tidal volumes in conventional ventilation — should be taken from considering the two studies together. Illness-severity scores were lower at randomization in the OSCAR study than in the OSCILLATE study. However, the control group in the OSCAR study had a rate of death of 41.1%, whereas the rate of death in the OSCILLATE study was 35%. Although the ventilation protocols in the control groups seem similar, in the OSCILLATE study, investigators were more successful in delivering low tidal volumes. In the OSCAR study, the delivered tidal volumes were just over 8 ml per kilogram of body weight. The original study by the ARDS Network[2] showed the importance of targeting a low tidal volume. Needham et al.[3] showed that ventilation with tidal volumes of less than 6.5 ml per kilogram was associated with a survival advantage, as compared with even modestly higher values (6.5 to 8.5 ml per kilogram). It would appear that the control groups in the OSCILLATE and OSCAR studies reveal a major difference in practice, which resulted in a survival difference.

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1. Young D, Lamb SE, Shah S et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013;368:806-13.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
3. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ 2012;344:e2124.

DOI: 10.1056/NEJMc1304344

TO THE EDITOR: In experimental models of lung failure, the use of HFOV improves oxygenation and reduces lung injury, as compared with low-tidal-volume ventilation.[1] However, neither the OSCILLATE study nor the OSCAR study was able to translate this benefit from bench to bedside. Two factors are at play. First, both the time of initiation of HFOV and the type of lung injury are crucial determinants of the potential for lung re-

cruitment. The inclusion of patients receiving mechanical ventilation for up to 1 week and the high prevalence of direct lung injury may have contributed to the reported lack of benefit for HFOV. Second, HFOV is a complex technique requiring high levels of expertise and is associated with a considerable learning curve. Although we note the efforts to train personnel at the experimental sites, for the studies to be credible, there needs to be a verifiable demonstration of skill in the use of HFOV by all operators.

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No potential conflict of interest relevant to this letter was reported.

1. Muellenbach RM, Kredel M, Said HM, et al. High-frequency oscillatory ventilation reduces lung inflammation: a large-animal 24-h model of respiratory distress. Intensive Care Med 2007;33:1423-33.

DOI: 10.1056/NEJMc1304344

TO THE EDITOR: We think that the methods that were used to set mean airway pressure in the OSCAR and OSCILLATE trials were sufficiently different to be clinically meaningful. In the OSCAR trial, the mean airway pressure was set at 5 cm of water above the pressure recorded in conventional ventilation, whereas it was set according to levels of the fraction of inspired oxygen in the OSCILLATE trial. Therefore, in the OSCILLATE trial, the mean airway pressure was greater in the HFOV group at day 1 than in the control group, and the difference persisted during the first week. We have found that the use of a mean airway pressure of more than 5 cm above the level of airway pressure recorded during conventional ventilation was not associated with better oxygenation but was associated with a decrease in cardiac output by worsening right ventricular function.[1] This mechanism probably occurred in patients in the OSCILLATE study, in which the HFOV group had higher use of vasopressors after initiation of the protocol than did the control group.

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No potential conflict of interest relevant to this letter was reported.

1. Guervilly C, Forel JM, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2012;40:1539-45.

DOI: 10.1056/NEJMc1304344

DR. FERGUSON AND COLLEAGUES REPLY: Different ventilatory strategies have varying consequences on many physiological and biologic processes, including gas exchange, hemodynamics, ventilator-induced lung injury, and patient comfort, which often makes it difficult to predict the effects of these strategies on outcome. Each of the correspondents highlights this fact and shows why clinical trials are necessary to weigh the positive and negative effects of different aspects of any given ventilatory strategy.

As discussed in our article, we agree with Liaudet and with Guervilly and colleagues that higher mean airway pressures in the HFOV group may have contributed to excess mortality. After the publication of the study by Guervilly et al., which suggested worsening right ventricular function on echocardiography with HFOV, the OSCILLATE steering committee discussed whether there should be any changes to the protocol.[1] Given the uncertain clinical relevance of their findings, the potential benefits of higher mean airway pressures in mitigating ventilator-induced lung injury, and expert recommendations underlying our protocol,[2] we did not change the protocol but recommended that investigators consider performing echocardiography in study participants receiving HFOV.

We agree with McDermid and Csányi-Fritz that increased sedation and fluid administration could have contributed to the increased mortality in the HFOV group, although the relative importance of this mechanism is unclear. Observational data such as those obtained in the SOAP study may be confounded by severity of illness. Indeed, data from randomized trials have shown that large differences in sedative administration were not associated with differences in mortality.[3]

We agree with MacDuff and Holland that the conventional ventilation strategy used in the control group in our study (i.e., low tidal volumes and higher PEEPs) may have contributed to our finding of better outcomes for conventional ventilation. However, we urge caution in comparing the outcomes in control groups across studies, since even subtle differences in methods may

have important implications. For example, in the OSCAR study, severity of illness was calculated on admission, whereas we used data obtained 24 hours before randomization, which may have resulted in systematic differences in scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II between the studies.

As Muellenbach and colleagues point out, both the timing of HFOV initiation and the expertise of the personnel using the device may have important implications. We specified that patients be enrolled within 72 hours after meeting study inclusion criteria, and we enlisted centers in which there was substantial experience in using HFOV. Although we cannot attest to the expertise of every clinician who cared for patients in the trial, we found no relationship between the number of patients studied per site (as a rough measure of experience) and mortality.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Fessler HE, Derdak S, Ferguson ND, et al. A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. Crit Care Med 2007;35:1649-54.
2. Guervilly C, Forel JM, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. Crit Care Med 2012;40:1539-45.
3. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92. [Erratum, JAMA 2013;309:237.]

DOI: 10.1056/NEJMc1304344

DR. YOUNG REPLIES: MacDuff and Holland suggest that the lower mortality in the OSCILLATE control group, which they attribute to the use of smaller tidal volumes in conventional ventilation than were used the OSCAR study, may have unmasked the harm that HFOV was causing. This may be the case, although there might also have been differences between the two control groups that were not captured in the severity scores, demographic characteristics, or other recorded data that would account for the differences.

In the OSCAR study, we spent a considerable amount of time training participating critical care staff in the use of HFOV. It would not have been appropriate to introduce a new mechanical ventilator to critical care units without this training, whether in the context of a trial or not. In clinical trials of interventions that require training, it is not uncommon to look at the results to see whether the effect size changes as units recruit more patients, suggesting a learning effect. We are currently looking into this issue.

Guervilly and colleagues suggest that in the OSCILLATE study, the higher mean airway pressure in the HFOV group than in the control group may account for the increased early use of vasoactive drugs in this group. In the OSCAR study, the mean pressure was not recorded in the control group, so we cannot determine whether it was the same as that in the HFOV group. There was no significant between-group difference in the use of vasoactive drugs in the OSCAR study, as recorded as the proportion of patients receiving these drugs.

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Since publication of his article, the author reports no further potential conflict of interest.

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Myths, Presumptions, and Facts about Obesity

TO THE EDITOR: Casazza et al. (Jan. 31 issue)[1] state that the common notion that "regularly eating (versus skipping) breakfast is protective against obesity" because people who skip breakfast may overeat later in the day is currently nothing more than a presumption. However, the evidence they cite in support of this statement is more complex than they intimate. Examination of this evidence implies overcompensation (with increased food consumption later in the day after having skipped breakfast), but also undercompensation depending on timing of meals.[2,3] In addition, Casazza and colleagues do not acknowledge the short-term nature of the available experimental research on which they focus exclusively. Several surveys and a longitudinal study have negatively correlated body-mass index (BMI) with the frequency of eating breakfast, and mul-

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013;368:806-13. DOI: 10.1056/NEJMoa1215716

Supplemental information for "High frequency oscillation for acute respiratory distress syndrome", Young D, Lamb S, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson B H, on behalf of the OSCAR collaborators.

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OSCAR Trial Collaborators

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Ethics committees approval numbers and ISRCTN number.

In the UK ethics committee approval for multi-centre studies is obtained from regional ethics committees and their approval covers all recruiting centres. Different regional ethics committees concentrate on different types of studies. The OSCAR protocol was reviewed by committees with particular expertise in studies involving patients unable to give informed consent. Approval for studies in Scotland has to be obtained separately from approval for studies in England, Wales and Northern Ireland.

Ethical approval was provided by the Scotland "A" and the Southampton and South West Hampshire multi-centre ethics review boards (MREC numbers 07/MRE00/73 and 07/HO502/98 respectively). Informed consent was obtained from the patients or from personal or nominated consultees (England and Wales) or Welfare Attorneys (Scotland) for the patients who lacked capacity.

The OSCAR study was registered with International Standard Randomised Controlled Trial Number Register (ISRCTN) reference number ISRCTN10416500.

Details of training of study centres

All units received training in HFOV before starting recruitment, and support through the trial. We employed a full-time medically qualified trainer for the first year of the study and two part-time experienced nurse trainers for a further 30 months.

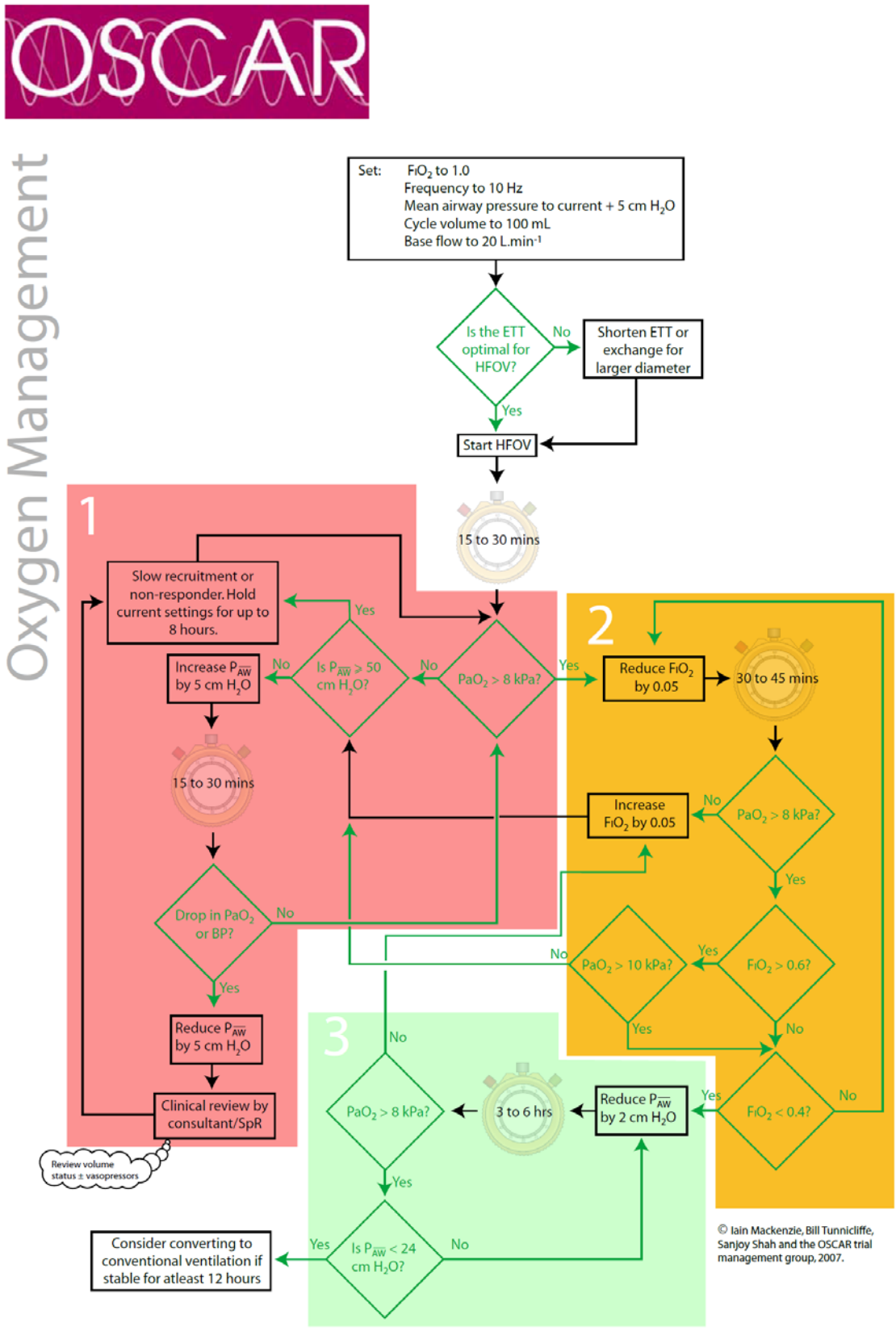
Written and computerised training materials including a study-specific detailed set-up and operating manual for the Novalung Metran R100 HFOV ventilator, training slide sets and training video were prepared. Most training was done on-site but this was supplemented with centralised training days and sessions in patient simulator suites in Oxford and Birmingham. Frequently-asked question lists and newsletters were prepared and distributed to centres.

Telephone advice on clinical or other problems was available at any time day or night from experienced senior clinicians. The company that supplied the ventilators (Inspiration Healthcare, Leicester, UK) provided a 24 hour telephone service for ventilator-related technical problems and supply of ventilator consumables.

Prior to starting recruitment, and during the first 42 months of the study, we trained a total of 2306 intensive care nurses, medical staff, physiotherapists and technicians using face-to-face teaching in 198 discrete training sessions.

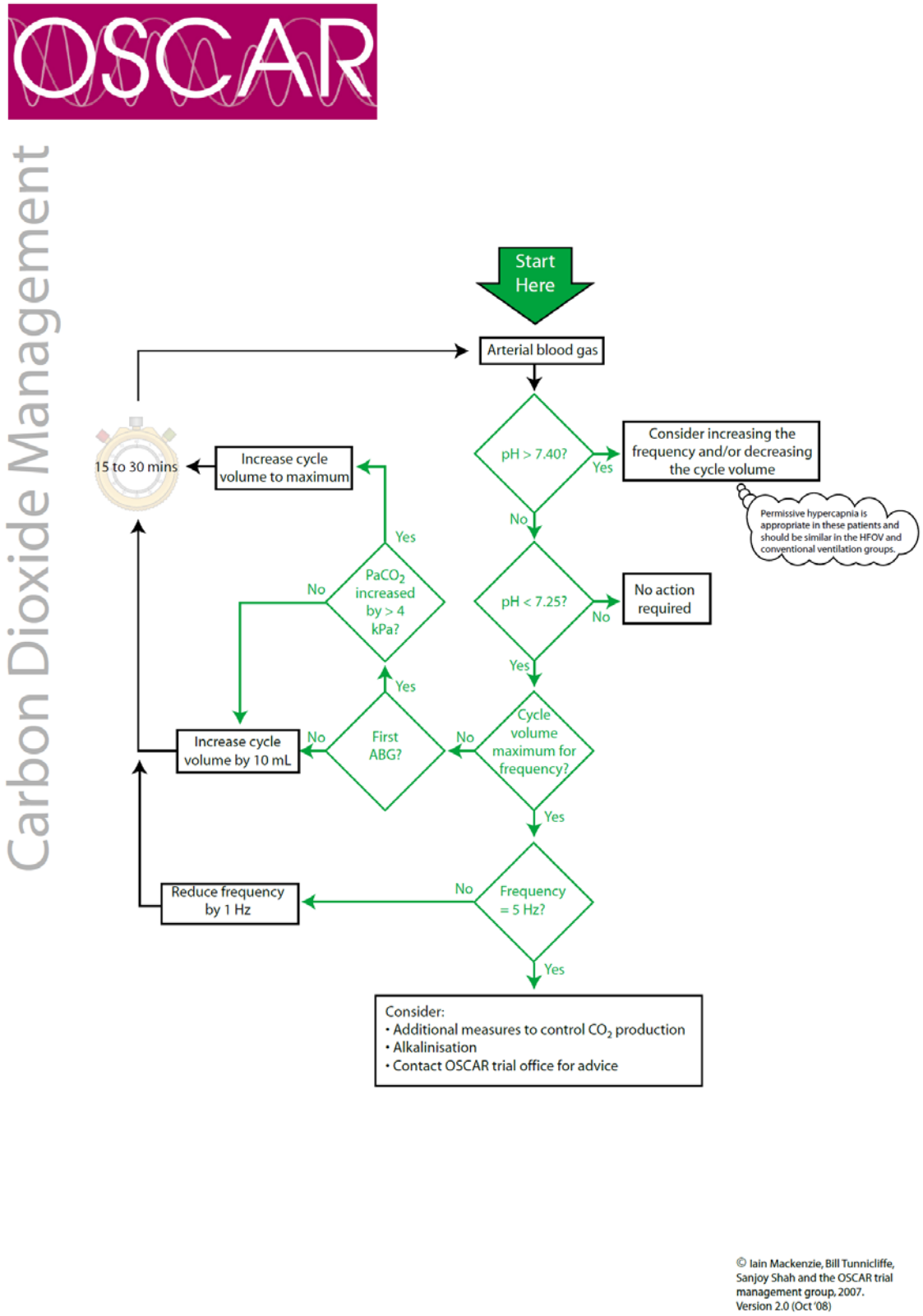
Oxygenation control algorithm

Figure S1: The oxygenation control algorithm. A version using mmHg units for blood gas tensions was also available.



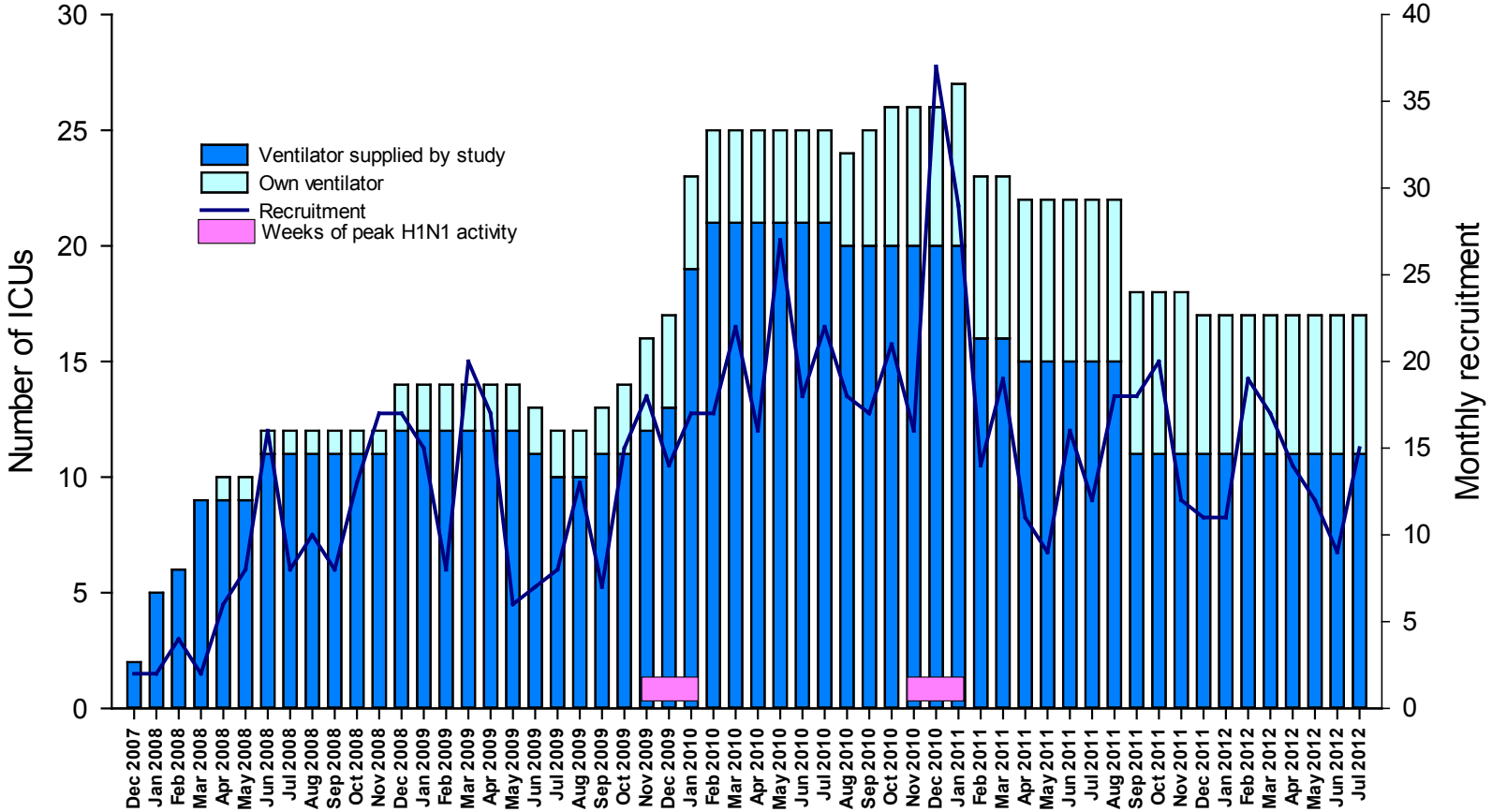
Carbon dioxide control algorithm

Figure S2: The carbon dioxide control algorithm. A version using mmHg units for blood gas tensions was also available.



Graphical summary of recruitment

Figure S3: Centres open to recruitment by month (vertical bars), divided into those centres where the ventilator was supplied by the study (dark blue) which had no previous experience with HFOV, and those who owned their own Novalung Metran R100 HFOV ventilator (pale blue) and had some experience with HFOV. Monthly recruitment is shown as a blue line. The two periods of peak H1N1 infections in the UK in the 2009-10 (data from UK-wide ICU surveillance) and 2010-11 (data from UK-wide primary care surveillance) winters are marked with pink bars.



Location and level of respiratory support in patients who died

Table S1: The table below gives the location and respiratory support in progress at time of death for all patients who died in hospital. Some patients died in hospital more than 30 days after randomisation, so the total number of deaths is greater than the number reported as 30 day mortality in the paper. All patients who died while on HFOV or mechanical ventilation were being treated on ICUs. In the HFOV ventilation group the sum of the percentages is less than 100% because of rounding.

	HFOV group (n=398, 196 in-hospital deaths)	Conventional mechanical ventilation group (n=397, 192 in-hospital deaths)
Died whilst on HFOV. n (% of in-hospital deaths)	80 (40.8%)	4 (2.1%)
Died on mechanical ventilation but not on HFOV. n (% of in-hospital deaths)	85 (43.4%)	159 (82.8%)
Died off mechanical ventilation but on an ICU. n (% of in-hospital deaths)	13 (6.6%)	9 (4.7%)
Died after ICU discharge but before discharge from an acute hospital. n (% of in-hospital deaths)	18 (9.1%)	20 (10.4%)

Details of arterial carbon dioxide tension ($PaCO_2$) in patients

Figure S4: The mean and standard deviation for $PaCO_2$ in patients on HFOV and on conventional mechanical ventilation, recorded at or near 8am each day, are shown for the first 14 days after randomisation. On day 14 only eight patients remained on HFOV, and summary data beyond this ceases to be meaningful.

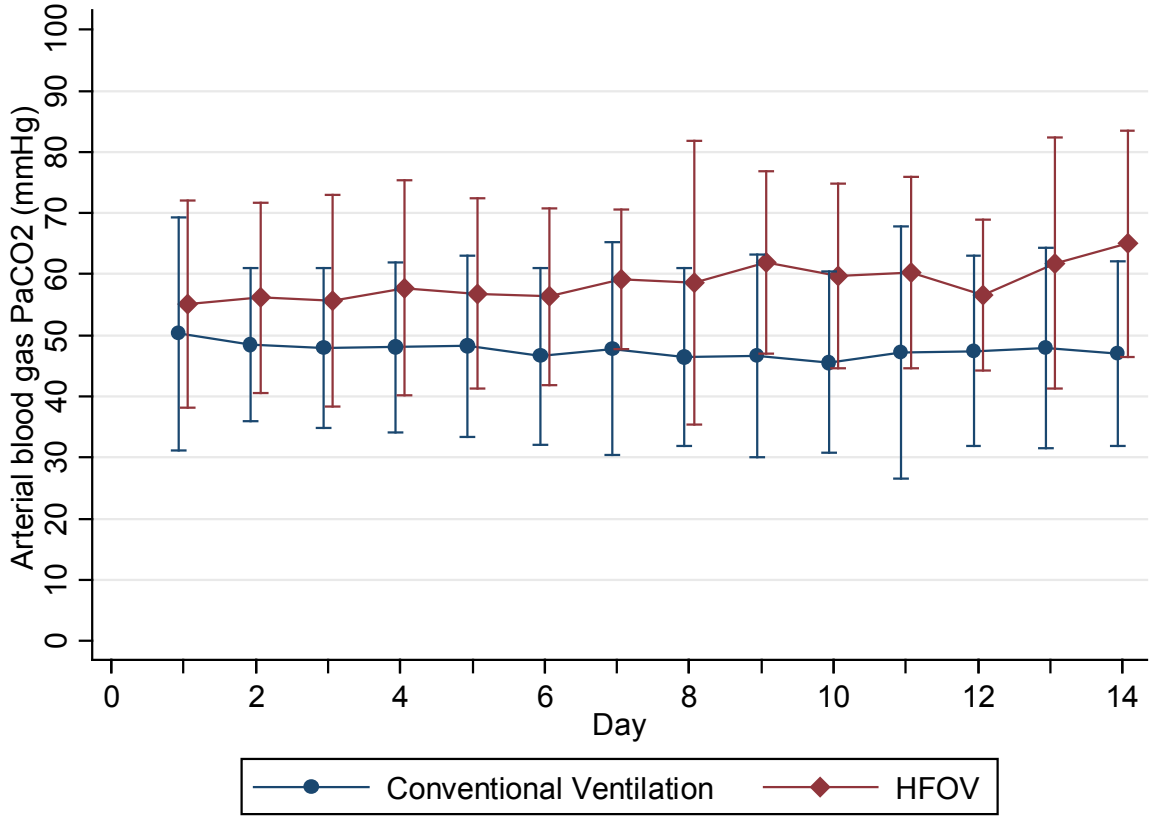
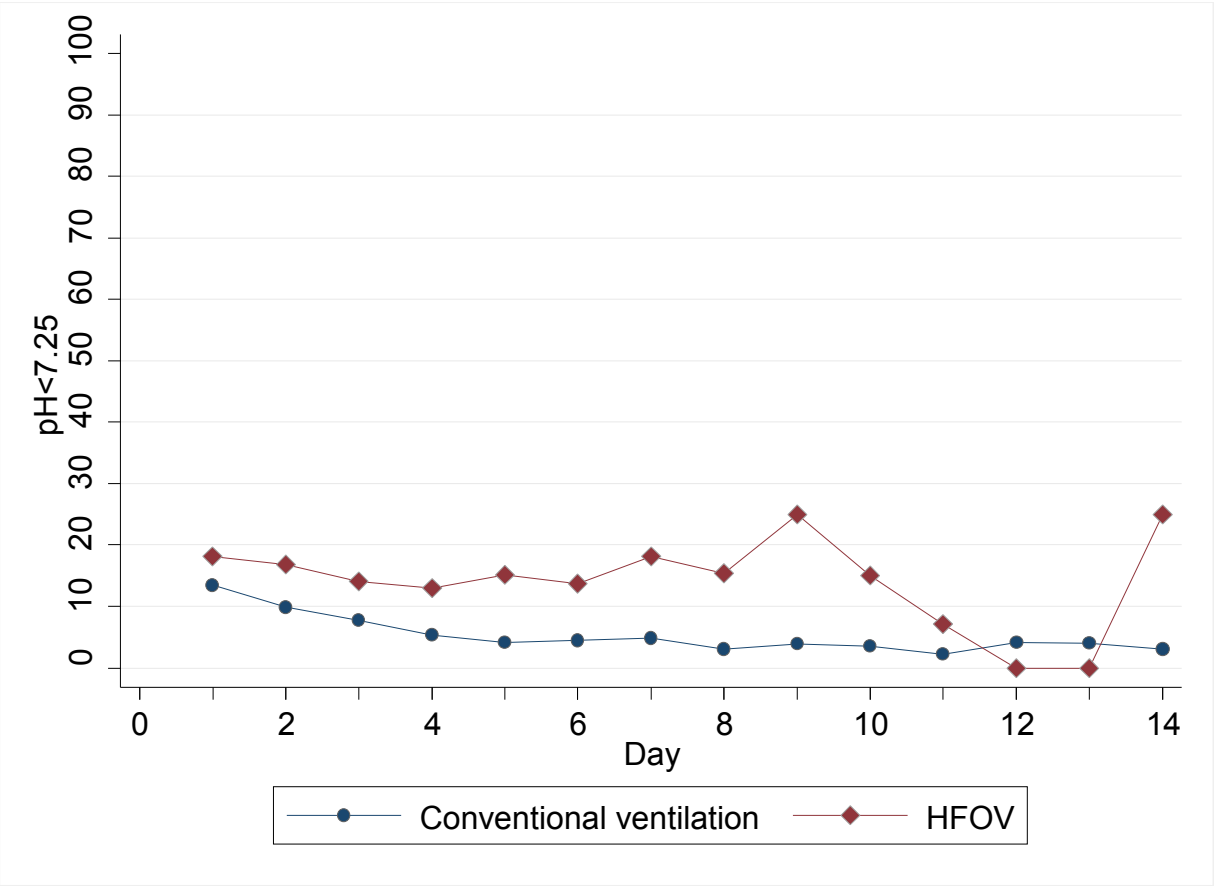


Figure S5: The percentage of all patients below the lower control limit of arterial pH (7.25) on the carbon dioxide control algorithm recorded at or near 8am each day for the HFOV group is shown for the first 14 days after randomisation. On day 14 only eight patients remained on HFOV, and summary data beyond this ceases to be meaningful. The percentage of patients in the conventional ventilation group with an arterial pH less than 7.25 is also shown.



In the early phases of the study we had several support calls about patients in whom the $PaCO_2$ rose rapidly after commencement of HFOV. Two of these were reported as serious adverse events (SAEs) by local investigators. In the first case the elevated $PaCO_2$ was felt to be one of three factors contributing to a “pulseless electrical activity” (PEA) cardiac arrest and in the second the $PaCO_2$ reached an unspecified extreme value. The first of these patients subsequently died whist on conventional mechanical ventilation, the second was discharged home.

The initial carbon dioxide control algorithm specified a 30 minute interval between blood gas estimations. To enable more rapid identification of this problem we changed this to 15-30 minutes. The modified algorithm (version 2) used for the majority of the study is shown on page 4 of this document.

The carbon dioxide control algorithm required the centres to contact the on-call clinician if at 5Hz and maximum cycle volume the patient had an arterial pH below 7.25. If the clinician received a call they would first check there were no impediments to ventilation (blocked endotracheal tube, pneumothorax etc). He would suggest techniques to reduce apparatus dead space and ensure the endotracheal tube was of adequate internal diameter. He would then suggest techniques to reduce spontaneous respiratory effort if this was thought to be contributory, using increased sedation or neuromuscular blocking drugs. He would recommend fever control. If this was unsuccessful the centre was advised to introduce a cuff leak. The use of cuff leak was recorded on the case report form. It was used in 30 of the HFOV group patients.

If the acidosis was primarily of metabolic origin alkalinisation was suggested.