

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 ( $\text{PaO}_2$ ) to the fraction of inspired oxygen ( $\text{FiO}_2$ ) 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  $\text{PaO}_2\text{:FiO}_2$  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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**T**HE 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,<sup>1</sup> and survivors may have functional limitations for years.<sup>2,3</sup> Although mechanical ventilation can initially be lifesaving in patients with ARDS, it can also further injure the patients' lungs and contribute to death.<sup>4</sup>

High-frequency oscillatory ventilation (HFOV) was first used experimentally in the 1970s to minimize the hemodynamic effects of mechanical ventilation.<sup>5</sup> 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<sup>6</sup> 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 ( $P_{aO_2}$ ) to the fraction of inspired oxygen ( $F_{iO_2}$ ) 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,  $P_{aO_2}:F_{iO_2}$  ratio ( $\leq 113$  mm Hg [15 kPa] or  $>113$  mm Hg), age ( $\leq 55$  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)<sup>7</sup> 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 ( $\text{PaCO}_2$ ) 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  $\text{PaCO}_2$  level (see the Supplementary Appendix).

The  $\text{PaO}_2$  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  $\text{FiO}_2$  level. If a patient reached a mean airway pressure of 24 cm of water, at an  $\text{FiO}_2$  level of 0.4 or less, with a  $\text{PaO}_2$  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  $\text{FiO}_2$  values that were used in the Acute Respiratory Distress Syndrome Network study.<sup>4</sup> 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.<sup>8</sup> 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.<sup>9,10</sup> 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,  $\text{PaO}_2\text{:FiO}_2$  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 ( $\pm$ SD) of  $2.0\pm 3.4$  days in the conventional-ventilation group and for  $2.5\pm 3.5$  days in the HFOV group ( $P=0.02$ ). Sedative drugs were used for  $8.5\pm 6.9$  days in the conventional-ventilation group and for  $9.4\pm 7.2$  days in the HFOV group ( $P=0.07$ ).

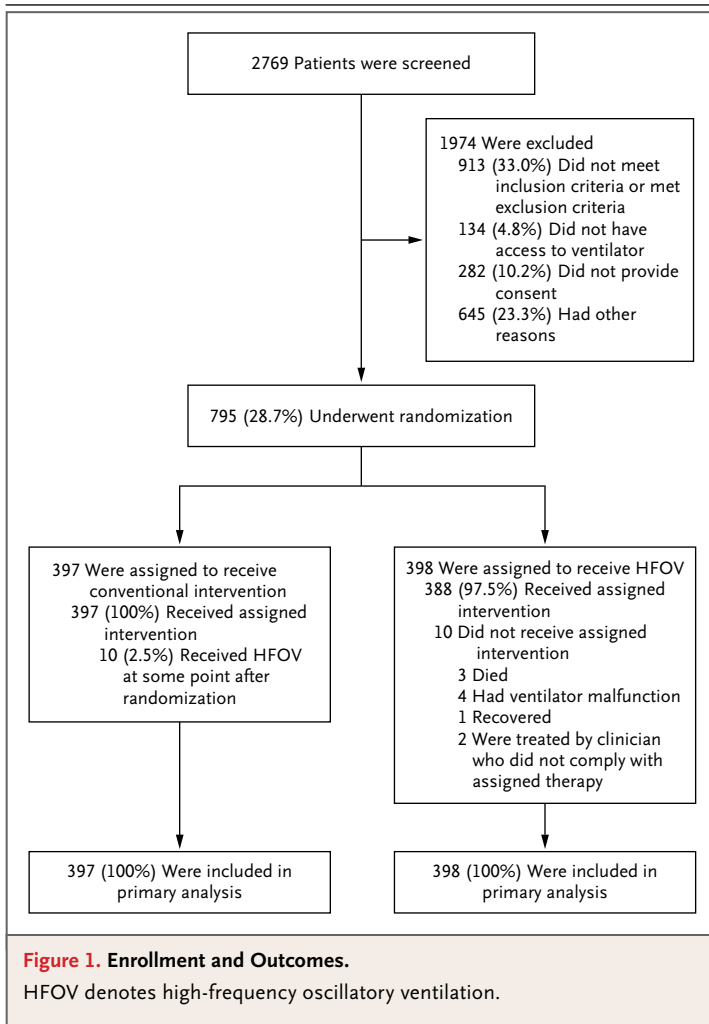
The patients had  $17.6\pm 8.8$  ventilator-free days in the conventional-ventilation group and  $17.1\pm 8.6$  ventilator-free days in the HFOV group ( $P=0.42$ ). Mechanical ventilation (including HFOV but excluding noninvasive ventilation) was used for  $14.1\pm 13.4$  days in the conventional-ventilation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

## 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  $\text{PaO}_2\text{:FIO}_2$  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  $16.1\pm 15.2$  days in the conventional-ventilation group and  $17.6\pm 16.6$  days in the HFOV group ( $P=0.18$ ); the total durations of hospital stay were  $33.1\pm 44.3$  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
PaO <sub>2</sub> :FiO <sub>2</sub> 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, FiO<sub>2</sub> fraction of inspired oxygen, and PaO<sub>2</sub> 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.<sup>11</sup>

‡ 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).

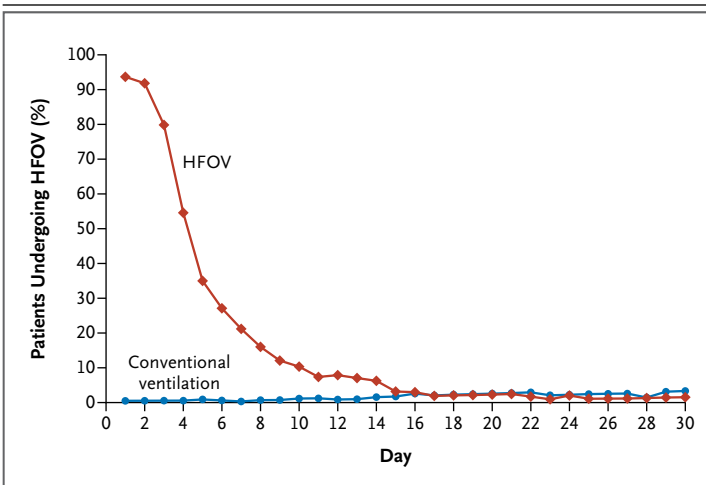
## DISCUSSION

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).<sup>12</sup> 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 PaO<sub>2</sub>:FiO<sub>2</sub> ratio of 113 mm Hg (15.1 kPa). The study-entry criterion was a PaO<sub>2</sub>:FiO<sub>2</sub> ratio of less than 200 mm Hg (26.7 kPa), which was in line with the agreed definition of ARDS,<sup>13</sup> but the additional requirement of a further 48 hours or more of mechanical ventilation may have excluded milder cases of ARDS. The average PaO<sub>2</sub>:FiO<sub>2</sub> ratio is nearly identical to the mean of 112 mm Hg reported in the recent systematic review of HFOV<sup>6</sup> and is similar to the mean values reported in studies of other treatments for ARDS.<sup>14–16</sup> 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.<sup>9,10</sup> 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<sub>2</sub> 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<sup>10</sup> but not in the smaller study<sup>9</sup> or the meta-analysis.<sup>6</sup> 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,<sup>17</sup> 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,<sup>6</sup> 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 <sub>2</sub> :FiO <sub>2</sub> ratio — mm Hg	192±77	154±61	212±69	163±66	217±69	166±63
Paco <sub>2</sub> — 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<sub>2</sub> 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.

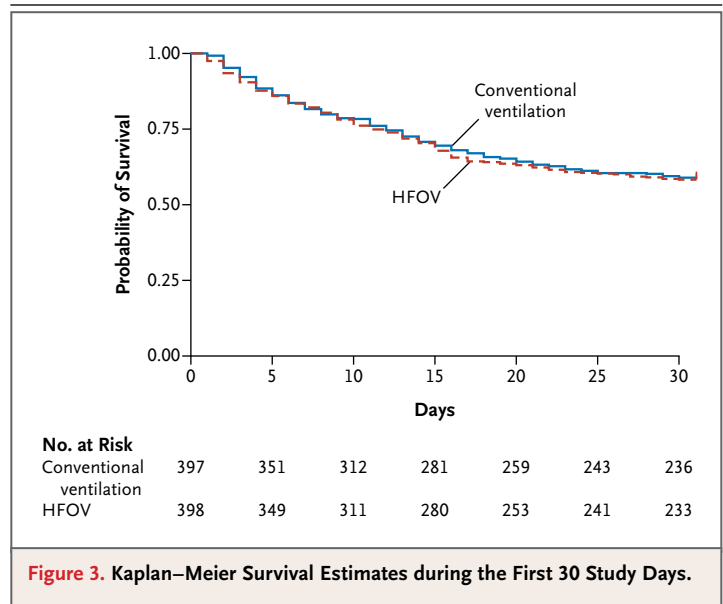
in the meta-analysis. Adding our results to the meta-analysis changes the estimated risk ratio from the pooled studies to 0.90 (95% CI, 0.76 to 1.07), indicating no significant benefit for HFOV.

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,<sup>9,10</sup> 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<sup>13</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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 re-expand 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.

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

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