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HIGH-FREQUENCY OSCILLATORY VENTILATION FOR THE PREVENTION OF CHRONIC LUNG DISEASE OF PREMATURITY

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ABSTRACT

Background There remains uncertainty concerning the safety and efficacy of high-frequency oscillatory ventilation as compared with those of conventional ventilation for the respiratory support of very preterm infants. We conducted a multicenter trial to determine whether early intervention with high-frequency oscillatory ventilation reduced mortality and the incidence of chronic lung disease among newborns with a gestational age of 28 weeks or less.

Methods We randomly assigned preterm infants with a gestational age of 23 to 28 weeks to either conventional ventilation or high-frequency oscillatory ventilation within one hour after birth. Randomization was stratified according to center and gestational age (23 to 25 weeks or 26 to 28 weeks).

Results A total of 400 infants were assigned to high-frequency oscillatory ventilation, and 397 were assigned to conventional ventilation. The composite primary outcome (death or chronic lung disease, diagnosed at 36 weeks of postmenstrual age) occurred in 66 percent of the infants assigned to receive high-frequency oscillatory ventilation and 68 percent of those in the conventional-ventilation group (relative risk in the group assigned to high-frequency oscillatory ventilation, 0.98; 95 percent confidence interval, 0.89 to 1.08). Similar proportions of infants died or had chronic lung disease in each gestational-age group. In both treatment groups treatment failure occurred in 10 percent of infants (relative risk in the group assigned to high-frequency oscillatory ventilation, 0.99; 95 percent confidence interval, 0.66 to 1.50). There were no significant differences between the groups in a range of other secondary outcome measures, including serious brain injury and air leak.

Conclusions The results obtained with high-frequency oscillatory ventilation and conventional ventilation do not differ significantly in the early treatment of respiratory disease in very preterm infants. Assessment of long-term effects will require additional follow-up. (N Engl J Med 2002;347:633-42.)

PULMONARY disease continues to be a major cause of illness and death in very preterm infants. Despite the introduction of a number of therapeutic interventions, the incidence of chronic lung disease remains high among such infants. Pulmonary immaturity, high ventilator pressure, and oxygen toxicity are major risk factors for chronic lung disease whose frequency could be reduced through the use of high-frequency oscillatory ventilation. Such ventilation involves the application of rapid oscillatory pressure — at 5 to 15 Hz, or 300 to 900 breaths per minute — superimposed on a continuous distending pressure.

Although studies in animals have shown that high-frequency oscillatory ventilation has a substantial advantage over conventional ventilation in terms of short-term pulmonary benefits,[1-4] the results of previous human trials comparing the two modes of ventilation remain inconclusive.[5-13] The most recent systematic review concluded that when high-frequency oscillatory ventilation was used with optimization of lung volume, there were significant reductions in the rate of death or oxygen dependency at 28 to 30 days (relative risk, 0.53; 95 percent confidence interval, 0.36 to 0.76) and in the frequency of chronic lung disease at 36 to 37 weeks of postmenstrual age (relative risk, 0.72; 95 percent confidence interval, 0.56 to 0.93).[14] The review noted no significant differences in the rates of complications, but a recent study once

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again raised the possibility that high-frequency oscillatory ventilation may be associated with an excess of severe periventricular hemorrhages.[11] However, previous trials have had limitations: small numbers of extremely preterm infants in the study cohorts, variable use of antenatal corticosteroids or postnatal surfactant, and delay in starting high-frequency oscillatory ventilation. Furthermore, interpretation of systematic reviews is complicated by the heterogeneity of the studies.

We conducted a multicenter, randomized trial comparing high-frequency oscillatory ventilation with conventional ventilation, in which ventilation by the assigned mode was instituted within 60 minutes after birth. Death or chronic lung disease at 36 weeks of postmenstrual age was the primary outcome measure.

METHODS

Study Population and Entry Criteria

A total of 25 centers participated in the study — 22 in the United Kingdom and 1 each in Australia, Ireland, and Singapore. To ensure that each center had adequate experience with high-frequency oscillatory ventilation, we required participating centers to have used this type of ventilatory support in a minimum of 20 infants before the study began. The quality of collected data was monitored and the statistical analyses were performed at the coordinating center (St. George's Hospital, London). Both the South Thames Multicentre Research Ethics Committee and the local research-ethics committee at each participating center approved the protocol.

Women at high risk of delivering an infant before 29 weeks of gestation were invited, before delivery, to participate in the trial, and oral or written assent was obtained. Randomization occurred either when delivery was imminent or immediately after the infant was born. Written confirmation of consent was obtained from one or both parents within 24 hours after the birth, as directed by the multicenter research-ethics committee. If consent was refused, the infant was excluded and the mode of ventilation was left to the discretion of the clinician.

Infants were eligible for the study if their gestational age was between 23 weeks and 28 weeks plus 6 days; if they were born in a participating center; if they required endotracheal intubation from birth; and if they required ongoing intensive care. Infants were excluded if they had to be transferred to another hospital for intensive care shortly after birth or if they had a major congenital malformation.

Assignment of Patients

After assent or consent had been obtained, infants were randomly assigned in blocks of four to either conventional ventilation or high-frequency oscillatory ventilation, with stratification according to gestational age (2 strata) and according to center (25 strata). Procedures were implemented to ensure balanced assignment within strata at each participating center. Each center kept a log of all eligible infants and reasons for nonrecruitment.

Treatment Strategies

Within one hour after birth, eligible infants were assigned to receive either conventional ventilation or high-frequency oscillatory ventilation as their primary mode of respiratory support. Unless the infant could be extubated electively, switching from the assigned mode of ventilation was permitted only during the first 120 hours after birth, if the clinical condition for a minimum of 1 hour met the criteria for treatment failure. These criteria were a partial pressure of oxygen (PaO_2) of less than 49 mm Hg in an infant receiving a fraction of inspired oxygen (FiO_2) of 1.0 following changes in the mean airway pressure or peak inspiratory pressure (PIP) or a partial pressure of carbon dioxide ($PaCO_2$) of more than 60 mm Hg despite interventions to improve ventilation, or both. If the infant still required ventilation after 120 hours of age, clinicians were free to use whichever mode of ventilation they wished. No changes in clinical management except those indicated below were specified as part of the trial. Conventional ventilation was delivered by time-cycled, pressure-limited ventilators starting with a rate of 60 breaths per minute and an inspiratory time of 0.4 second. Subsequently, ventilator settings were adjusted at the discretion of the attending clinician to maintain a PaO_2 between 49 and 75 mm Hg and a $PaCO_2$ between 34 and 53 mm Hg. High-frequency oscillatory ventilation, with optimization of lung volume, was delivered by one of three models of high-frequency oscillator (the Dräger Babylog 8000, the SensorMedics 3100A, or the SLE 2000HFO), all of which have been shown to have similar performance characteristics at the frequencies recommended in this trial.[15] Ventilation was begun at a mean airway pressure of 6 to 8 cm of water and a frequency of 10 Hz, and the amplitude was increased until the infant's chest was seen to be "bouncing." The ratio of inspiration to expiration was either fixed at 1:1 (with the Dräger or SLE ventilator) or 1:2 (with the SensorMedics ventilator), in accordance with the manufacturers' recommendations. The FiO_2 was initially set to ensure adequate oxygenation (PaO_2, >48 mm Hg), and when the FiO_2 was greater than 0.3, the mean airway pressure was increased by 0.5 to 1.0 cm of water every 10 to 15 minutes[16] until it was possible to decrease the FiO_2. The FiO_2 was reduced to 0.3 before the mean airway pressure was decreased, provided that the lungs were not hyperinflated (a condition defined by the flattening of the diaphragm below the margin of the ninth rib on chest radiography). Settings were then adjusted to maintain a PaO_2 between 49 and 75 mm Hg and a $PaCO_2$ between 34 and 53 mm Hg. Oxygenation was managed by adjustment of the mean airway pressure and the FiO_2; $PaCO_2$ was managed by adjustment of the oscillatory amplitude, but if difficulties in the management of the $PaCO_2$ persisted after a change in the amplitude alone, the ventilator frequency was also adjusted. If pulmonary interstitial emphysema developed, the strategy was changed to one of low volume and high FiO_2 with the reduction in the mean airway pressure to the lowest level compatible with a PaO_2 of 49 to 75 mm Hg, even if this strategy resulted in an increase in the FiO_2 to the range of 0.7 to 0.9. No simultaneous positive-pressure breathing was used.

The protocol recommended that infants receive exogenous surfactant as soon as possible after birth. A subsequent dose (given approximately 12 hours later) was recommended for infants receiving conventional ventilation if the FiO_2 was greater than 0.3 and for infants receiving high-frequency oscillatory ventilation if the mean airway pressure was greater than 10 cm of water.

Ultrasonographic scanning of the brain was performed less than 4 hours after birth, at 3, 7, and 28 days after birth, and at discharge. All abnormal scans and a random sample of 20 percent of normal scans at 7 and 28 days were reevaluated by an independent observer who was unaware of the mode of ventilation used. If the rating of this observer differed from the original rating of the center, all scans for that infant were jointly evaluated by that observer and another blinded independent observer in order to assign a rating.

We collected neonatal inpatient data from birth to discharge. Infants who survived to discharge are currently being followed until 24 months of corrected gestational age and monitored for long-term respiratory and neurologic outcomes.

Definition of Outcomes and Sample-Size Calculations

The primary outcome measure was a composite of death or chronic lung disease (defined by a dependence on supplemental oxygen) at 36 weeks of postmenstrual age. Secondary outcome measures were the age at death, the age at hospital discharge, major ab-

normality on cranial ultrasonography, air leak, failure of treatment, failure on hearing testing, necrotizing enterocolitis, patent ductus arteriosus requiring treatment, treatment with postnatal systemic corticosteroids, pulmonary hemorrhage, and retinopathy of prematurity. A sample of 800 to 1200 infants was needed, given the assumptions that 30 percent of the study population would have a gestational age of 23 to 25 weeks and 70 percent would have a gestational age of 26 to 28 weeks and that the incidence of the primary outcome would be 75 percent for the lower-gestational-age group and 48 percent for the higher-gestational-age group. With a sample of this size, the study had 90 percent power (at a significance level of 0.05) to detect a difference between treatment groups of 9 to 11 percentage points.

Statistical Analysis

An independent committee reviewed statistical analyses performed 12 and 18 months after recruitment began and found no reason to stop the trial early. Analyses were adjusted to preserve an overall level of significance of 0.05. For the secondary outcomes (both main effects and interactions), we used the Bonferroni method to correct for multiple testing,[17] which resulted in the use of a P value of 0.004 to indicate significance. All reported P values are uncorrected unless otherwise stated.

Unadjusted relative risks or hazard ratios, as appropriate, with 95 percent confidence intervals were calculated to estimate the relative effect of high-frequency oscillatory ventilation as compared with that of conventional ventilation for all outcomes. Logistic regres-

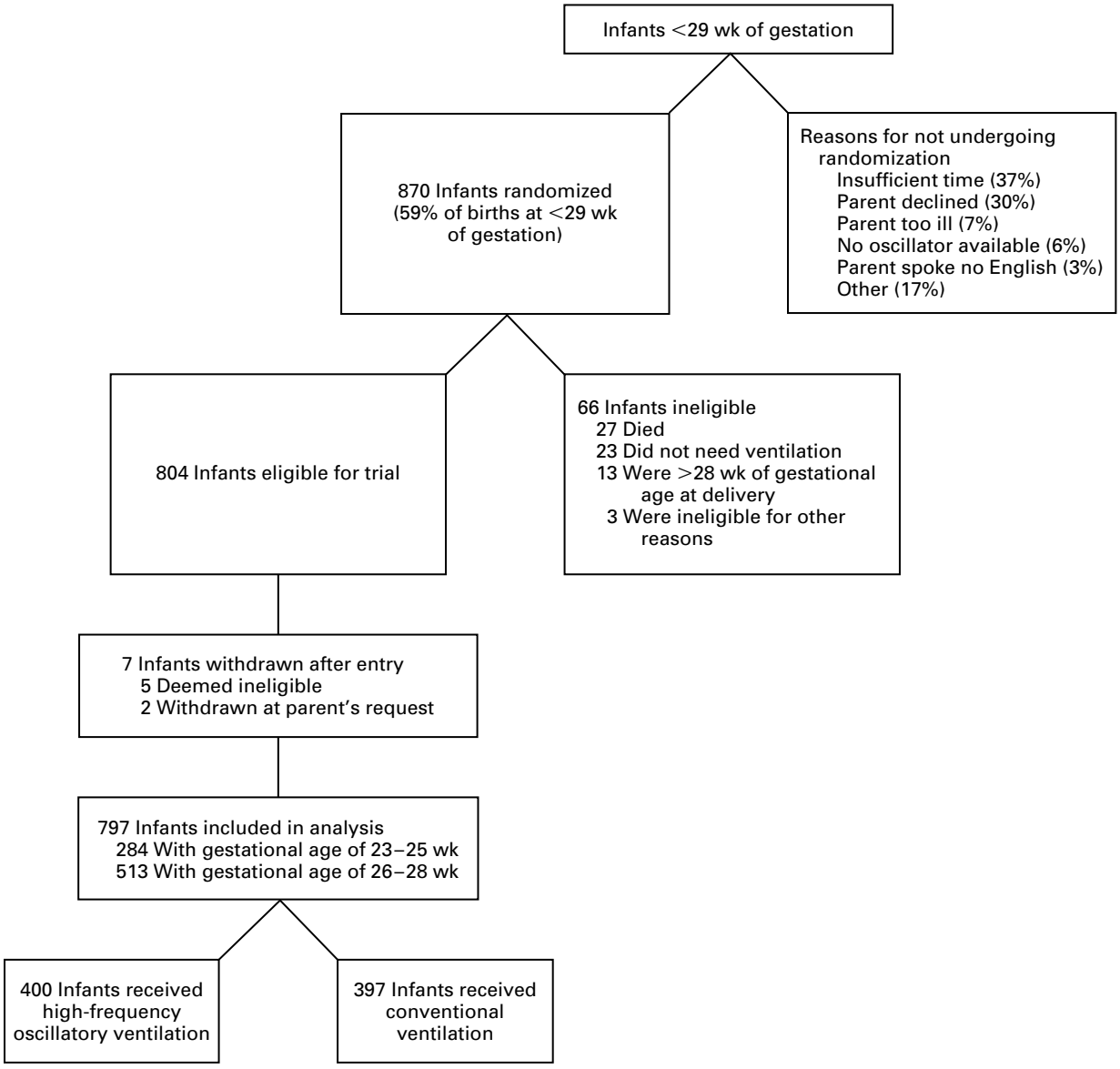

Figure 1. Recruitment and Randomization of Infants.

TABLE 1. CHARACTERISTICS OF THE MOTHERS.

CHARACTERISTIC	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION
Age (yr)*	29±6.4	29±6.1
	no./total no. (%)	
Age <19 yr	17/363 (5)	20/351 (6)
Race		
White	290/363 (80)	276/353 (78)
Black	35/363 (10)	31/353 (9)
Other	38/363 (10)	46/353 (13)
Smoking during pregnancy	95/334 (28)	86/321 (27)
Preexisting or pregnancy-induced diabetes	11/364 (3)	7/351 (2)
Pregnancy-induced hypertension requiring treatment with antihypertensive agents	53/357 (15)	65/340 (19)
Preexisting hypertension	11/362 (3)	19/346 (5)
Hyperthyroidism or hypothyroidism	2/363 (1)	7/349 (2)
Antenatal corticosteroids		
Any antenatal corticosteroids	329/363 (91)	324/351 (92)
Completed courses†		
Single	231/324 (71)	225/319 (71)
Multiple	44/324 (14)	42/319 (13)
Complete courses with optimal timing‡		
Single	106/311 (34)	84/311 (27)
Multiple	29/311 (9)	27/311 (9)
Antepartum hemorrhage§	37/361 (10)	32/350 (9)
Rupture of membranes		
Prolonged interval (>24 hr) between rupture and delivery	117/360 (32)	95/347 (27)
Rupture at <22 wk of gestation	12/360 (3)	11/346 (3)
Proven chorioamnionitis¶	45/353 (13)	41/340 (12)
Tocolytic drugs used	87/357 (24)	82/344 (24)
Transfer to study hospital for delivery	145/357 (41)	135/343 (39)
Cesarean section		
After labor	75/364 (21)	64/353 (18)
Without labor	134/364 (37)	125/353 (35)

*Plus–minus values are means ±SD.

†A complete course consisted of a total of 24 mg of dexamethasone or betamethasone divided into two to four doses within a 48-hour period.

‡Optimal timing was defined as less than 48 hours before birth and less than 7 days after the previous dose.

§Data are for antepartum hemorrhage requiring obstetrical intervention or abruptio placentae with concealed hemorrhage.

¶Proven chorioamnionitis was defined by one of the following: fever in the mother and a serum C-reactive protein level in the mother of more than 50 mg per liter, a positive bacterial culture of amniotic fluid, or histopathological findings compatible with chorioamnionitis.

sion or Cox regression was used to investigate treatment effects, with the use of gestational age (23 to 25 weeks or 26 to 28 weeks) and location (United Kingdom and Ireland; Australia; or Singapore) as covariates. Interaction terms were fit in the model in order to assess differences in treatment effects according to gestational age and location. Base-line variables with the potential to be important prognostic factors were identified in advance of the analysis. We decided to include them in the model only if a clinically important imbalance was observed. All statistical analyses were performed according to the intention-to-treat principle, with the use of Stata software.[18]

RESULTS

Base-Line Data

Between August 1998 and January 2001, 870 infants underwent randomization; 804 were subsequently enrolled in the trial, and data from 797 were analyzed (Fig. 1). Of the 66 infants not enrolled, 33 were originally assigned to receive conventional ventilation and 33 to receive high-frequency oscillatory ventilation.

TABLE 2. CHARACTERISTICS OF THE INFANTS.

CHARACTERISTIC	INFANTS BORN AT 23–25 WK OF GESTATION		INFANTS BORN AT 26–28 WK OF GESTATION	
	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION
Birth weight — g*	704±127	710±131	926±212	942±220
Mean gestational age — wk	24.9	24.7	27.4	27.4
Birth weight standard-deviation score†				
Mean	−0.41	−0.36	−0.75	−0.68
Range	−3.56 to 1.70	−2.72 to 2.17	−3.64 to 2.41	−3.72 to 1.94
Male sex — no./total no. (%)	83/148 (56)	83/136 (61)	123/252 (49)	139/261 (53)
Multiple birth — no./total no. (%)	29/148 (20)	38/136 (28)	64/252 (25)	59/261 (23)
Twins	22/29 (76)	29/38 (76)	49/64 (77)	49/59 (83)
Triplets	7/29 (24)	9/38 (24)	13/64 (20)	8/59 (14)
Quadruplets	0/29	0/38	2/64 (3)	2/59 (3)
Heart rate ≤100 beats per min at 5 min — no./total no. (%)	19/147 (13)	16/133 (12)	25/248 (10)	21/256 (8)
Apgar score <7 at 5 min — no./total no. (%)	42/145 (29)	28/132 (21)	31/241 (13)	38/250 (15)
External cardiac massage or epinephrine at resuscitation — no./total no. (%)	15/146 (10)	19/133 (14)	17/249 (7)	17/256 (7)
Surfactant given — no./total no. (%)	143/148 (97)	134/136 (99)	240/252 (95)	252/261 (97)
Time to first dose				
Median — min	29	25	25	28
<1 hr — no./total no. (%)	112/141 (79)	111/133 (83)	187/239 (78)	183/252 (73)
1–2 hr — no./total no. (%)	16/141 (11)	12/133 (9)	28/239 (12)	46/252 (18)
Type of surfactant — no./total no. (%)				
Poractant alfa‡	70/141 (50)	61/133 (46)	104/29 (42)	102/252 (40)
Beractant‡	67/141 (48)	67/133 (50)	129/29 (52)	141/252 (56)
Pumactant‡	7/141 (5)	7/133 (5)	13/29 (5)	15/252 (6)
Combination§	3/141 (2)	2/133 (2)	7/239 (3)	6/252 (2)
Prophylactic indomethacin	14/148 (9)	7/135 (5)	25/251 (10)	21/259 (8)

*Plus–minus values are means ±SD.

†The standard-deviation score is calculated as the birth weight (in grams) minus the mean birth weight for gestational age (in grams) divided by the standard deviation of birth weight for gestational age (in grams).

‡Data include those who had more than one type of surfactant.

§One hospital had a policy of giving a combination of surfactants.

The two treatment groups were well balanced in terms of maternal characteristics (Table 1). A total of 91 percent of the women received antenatal corticosteroids. The groups were also closely matched in terms of characteristics of the infants (Table 2): 96 percent of infants were given surfactant-replacement therapy a median of 28 minutes after birth (range, 0 to 1232).

Primary Outcome

The composite primary outcome of death or chronic lung disease (defined by a dependence on supplemental oxygen) at 36 weeks of postmenstrual age occurred in 66 percent of infants assigned to high-frequency oscillatory ventilation and 68 percent of those assigned to conventional ventilation ($P=0.71$) (Table 3). Similar proportions of infants died (25 percent of those receiving high-frequency oscillatory ventilation vs. 26 percent of those receiving conventional ventilation) (Fig. 2) or had chronic lung disease (41 percent in each group). When the analysis was stratified according to gestational age, there were similar findings with respect to the primary outcome and the frequency of each component ($P=0.46$ for the interaction between gestational age and mode of ventilation). Overall, 33 percent of the infants were alive without dependence on supplemental oxygen at 36 weeks of postmenstrual age: 12 percent of those who were 23 to 25 weeks of gestational age and 45 percent of those who were 26 to 28 weeks of gestational age. There were no significant differences in treatment effects among locations ($P=0.19$ for the interaction between location and mode of ventilation).

Secondary Outcomes

The proportions of infants with each of the specified secondary outcomes were also similar in the two groups (Table 3). In particular, criteria for treatment failure were met in 10 percent of the infants in each group. None of the rates of the secondary outcomes

TABLE 3. PRIMARY AND SECONDARY OUTCOMES.

OUTCOME	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION	RELATIVE RISK (95% CI)*
Primary outcome — no./total no. (%)†			
All infants	265/400 (66)	268/397 (68)	0.98 (0.89–1.08)
Dead	100/400 (25)	105/397 (26)	
Alive, with chronic lung disease	165/400 (41)	163/397 (41)	
Alive, without chronic lung disease	135/400 (34)	129/397 (32)	
Infants 23–25 wk of gestational age	130/148 (88)	119/136 (88)	1.00 (0.92–1.10)
Dead	61/148 (41)	60/136 (44)	
Alive, with chronic lung disease	69/148 (47)	59/136 (43)	
Alive, without chronic lung disease	18/148 (12)	17/136 (12)	
Infants 26–28 wk of gestational age	135/252 (54)	149/261 (57)	0.94 (0.80–1.10)
Dead	39/252 (15)	45/261 (17)	
Alive, with chronic lung disease	96/252 (38)	104/261 (40)	
Alive, without chronic lung disease	117/252 (46)	112/261 (43)	
Secondary outcomes			
All infants			
Age at death — days			
Median	6	6	0.85 (0.64–1.13)
Interquartile range	1–19	2–19	
Duration of hospital stay for survivors — days			
Median	94	89	
Interquartile range	73–114	70–112	
Failure of treatment — no./total no. (%)	41/400 (10)	41/397 (10)	0.99 (0.66–1.50)
Air leak — no./total no. (%)	64/399 (16)	72/395 (18)	0.88 (0.65–1.20)
Pulmonary hemorrhage (requiring change in ventilator settings) — no./total no. (%)	44/395 (11)	55/390 (14)	0.79 (0.55–1.14)
Postnatal systemic corticosteroids — no./total no. (%)	104/339 (31)	94/340 (28)	1.11 (0.88–1.40)
Patent ductus arteriosus requiring treatment — no./total no. (%)	137/399 (34)	129/394 (33)	1.05 (0.86–1.28)
Major cerebral abnormality — no./total no. (%)	54/393 (14)	75/393 (19)	0.72 (0.52–0.99)
Retinopathy of prematurity (≥stage 2) — no./total no. (%)	43/400 (11)	42/396 (11)	1.01 (0.68–1.51)
Failed hearing test — no./total no. (%)	29/136 (21)	33/151 (22)	0.98 (0.63–1.52)
Necrotizing enterocolitis — no./total no. (%)	47/394 (12)	33/393 (8)	1.42 (0.93–2.17)
Infants 23–25 wk of gestational age			
Age at death — days			
Median	4	4	0.82 (0.57–1.20)
Interquartile range	1–16	2–13	
Duration of hospital stay for survivors — days			
Median	114	109	
Interquartile range	97–137	94–135	
Failure of treatment — no./total no. (%)	20/148 (14)	18/136 (13)	1.02 (0.56–1.85)
Air leak — no./total no. (%)	33/148 (22)	36/135 (27)	0.84 (0.55–1.26)
Pulmonary hemorrhage (requiring change in ventilator settings) — no./total no. (%)	23/146 (16)	37/133 (28)	0.57 (0.36–0.90)
Postnatal systemic corticosteroids — no./total no. (%)	56/111 (50)	45/97 (46)	1.09 (0.82–1.44)
Patent ductus arteriosus requiring treatment — no./total no. (%)	61/148 (41)	58/135 (43)	0.96 (0.73–1.26)
Major cerebral abnormality — no./total no. (%)‡	24/143 (17)	34/132 (26)	0.65 (0.41–1.04)
Retinopathy of prematurity (≥stage 2) — no./total no. (%)	27/148 (18)	25/135 (19)	0.99 (0.60–1.61)
Failed hearing test — no./total no. (%)	8/35 (23)	11/32 (34)	0.66 (0.31–1.44)
Necrotizing enterocolitis — no./total no. (%)	16/145 (11)	15/134 (11)	0.99 (0.51–1.92)
Infants 26–28 wk of gestational age			
Age at death — days			
Median	6	8	0.82 (0.52–1.27)
Interquartile range	2–23	4–28	
Duration of hospital stay for survivors — days			
Median	81	80	
Interquartile range	68–102	65–103	
Failure of treatment — no./total no. (%)	21/252 (8)	23/261 (9)	0.95 (0.54–1.66)
Air leak — no./total no. (%)	31/251 (12)	36/260 (14)	0.89 (0.57–1.40)
Pulmonary hemorrhage (requiring change in ventilator settings) — no./total no. (%)	21/249 (8)	18/257 (7)	1.20 (0.66–2.20)
Postnatal systemic corticosteroids — no./total no. (%)	48/228 (21)	49/243 (20)	1.04 (0.73–1.49)
Patent ductus arteriosus requiring treatment — no./total no. (%)	76/251 (30)	71/259 (27)	1.10 (0.84–1.45)
Major cerebral abnormality — no./total no. (%)	30/250 (12)	41/261 (16)	0.76 (0.49–1.18)
Retinopathy of prematurity (≥stage 2) — no./total no. (%)	16/252 (6)	17/261 (7)	0.97 (0.50–1.89)
Failed hearing test — no./total no. (%)	21/101 (21)	22/119 (18)	1.12 (0.66–1.92)
Necrotizing enterocolitis — no./total no. (%)	31/249 (12)	18/259 (7)	1.79 (1.03–3.12)

*Relative risks are for the infants receiving high-frequency oscillatory ventilation as compared with those receiving conventional ventilation. CI denotes confidence interval.

†Data are for infants at 36 weeks of postmenstrual age.

‡Data are for infants with intraventricular hemorrhage with ventricular dilatation or any parenchymal hemorrhage or cystic changes.

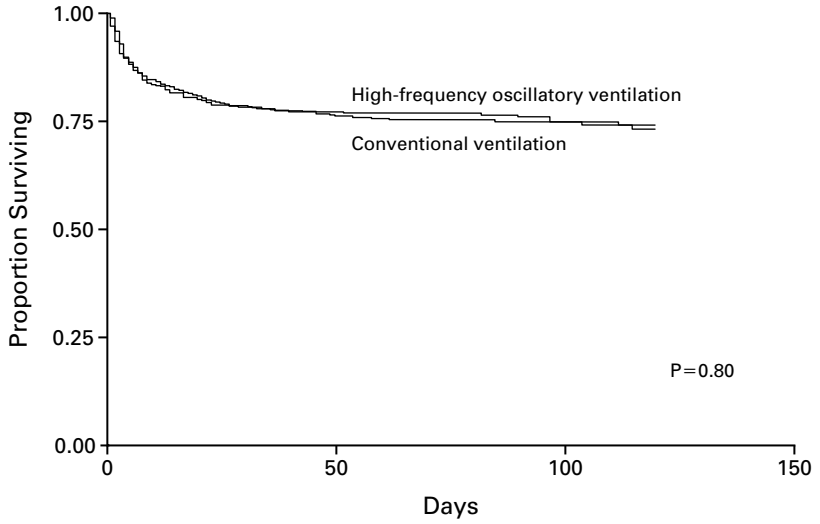

Figure 2. Kaplan–Meier Survival Curves for Infants Receiving Conventional Ventilation and Infants Receiving High-Frequency Oscillatory Ventilation.

differed significantly between the two gestational-age categories (Table 3).

Respiratory Outcomes

Infants who were randomly assigned to either treatment group received ventilation for a median of 7 days (interquartile range, 3 to 21 among infants assigned to high-frequency oscillatory ventilation and 2 to 20 among those assigned to conventional ventilation; P=0.58). Infants received high-frequency oscillatory ventilation for a median of three days (interquartile range, one to six), since the majority were switched to conventional ventilation for weaning. There were no significant differences in the frequency of major acute cardiorespiratory complications. Similar proportions in the two groups were receiving supplemental oxygen at 40 weeks of postmenstrual age (41 percent among infants receiving high-frequency oscillatory ventilation vs. 39 percent among those receiving conventional ventilation, P=0.54). Systemic corticosteroids were used for weaning from the ventilator in 31 percent of the infants receiving high-frequency oscillatory ventilation and 28 percent of those receiving conventional ventilation (P=0.37). Data relating to physiological variables including the mean airway pressure, FiO_2, $PaCO_2$, PaO_2, pH, and oxygen index are shown in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

Other Outcomes

The median age at death in the infants who died in each group was 6 days, and 15 percent of deaths in infants receiving high-frequency oscillatory ventilation (15 of 100) and 18 percent of those in infants receiving conventional ventilation (19 of 105) occurred after 28 days. The median duration of the hospital stay was similar in the two groups (Table 3), and the median postmenstrual age at discharge was 39.7 weeks among infants receiving high-frequency oscillatory ventilation (interquartile range, 37.6 to 42.7) and 39.0 weeks among those receiving conventional ventilation (interquartile range, 37.4 to 42.0).

Three variables were used as surrogate markers for long-term disability: abnormalities detected on cranial ultrasonography, retinopathy of prematurity, and adequacy of hearing. Targeted hearing screening before discharge occurred in only 10 of 25 centers. The predefined rate of serious abnormalities on cranial ultrasonography (parenchymal bleeding, ventriculomegaly, or parenchymal cysts) was lower in the group receiving high-frequency oscillatory ventilation (uncorrected P=0.04, Bonferroni-corrected P=0.44) (Table 4), but the rates of retinopathy and hearing loss were similar (Table 3). Stratification of the findings on cranial ultrasonography according to gestational age and postnatal age (Table 4) demonstrated no significant differences in the proportion of infants with abnormalities.

Type of Ventilator

Of the 397 infants in the conventional-ventilation group, 193 received ventilation with the use of the SLE 2000 or 2000HFO, 192 with the Dräger Babylog 8000, and 12 with other ventilators. By two hours of age, 10 infants randomly assigned to high-frequency

ventilation had died or had been extubated. Among the remaining infants, ventilation was provided for 187 infants with the SLE 2000HFO, for 165 with the Dräger Babylog 8000, and for 38 with the SensorMedics 3100A. We performed a prespecified analysis of the group receiving high-frequency oscillatory ventilation stratified according to the type of oscillator. There was no policy of choosing a particular model of ventilator according to the severity of the infant's initial respiratory illness.

The proportion of infants receiving high-frequency oscillatory ventilation in whom the primary outcome occurred varied according to the model of ventilator: 64 percent for those treated with the SLE ventilator, 64 percent for those treated with the Dräger ventilator, and 89 percent for those treated with the SensorMedics ventilator (uncorrected $P=0.004$, Bonferroni-corrected $P=0.04$ for the three-way comparison). Because of the small number of infants who received ventilation with the SensorMedics machine, it was not possible to perform a full multifactorial analysis, so an analysis was performed that used principal-component scores to adjust for base-line differences. This analysis showed that the difference in the frequency of the primary outcome between infants treated with the SensorMedics ventilator and those treated with either of the other two models remained after base-line differences had been accounted for. Full details appear in Supplementary Appendix 2 (available with the full text of this article at http://www.nejm.org).

DISCUSSION

In our large trial comparing high-frequency oscillatory ventilation with conventional ventilation, there was no significant difference between the two modes of ventilation in terms of the primary outcome measure, death or chronic lung disease, defined as a dependence on supplemental oxygen at a postmenstrual age of 36 weeks. Despite concern about an association between the use of high-frequency oscillatory ventilation and increased risks of air leak and abnormalities on ultrasonography of the brain,[14] such a relation was not observed in our study.

A strong evidence base does not exist with respect to the benefit or risk of the early use of high-frequency oscillatory ventilation in the treatment of respiratory disease in very preterm infants. In our study, steps were taken to reduce the risk of lung disease; more than 90 percent of mothers had received antenatal corticosteroids, and 96 percent of infants received postnatal surfactant. Ventilation by the assigned mode was initiated within one hour after birth, and the study had adequate power to exclude clinically important differences.

We initiated high-frequency oscillatory ventilation

TABLE 4. FINDINGS ON CRANIAL ULTRASONOGRAPHY.*

VARIABLE	INFANTS 23–25 WK OF GESTATIONAL AGE			INFANTS 26–28 WK OF GESTATIONAL AGE		
	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION	RELATIVE RISK (95% CI)	HIGH-FREQUENCY OSCILLATORY VENTILATION	CONVENTIONAL VENTILATION	RELATIVE RISK (95% CI)
	no./total no. (%)			no./total no. (%)		
Abnormality on early scan (birth–14 days)						
None	78/143 (55)	66/131 (50)	1.08 (0.86–1.36)	180/247 (73)	176/261 (67)	1.08 (0.96–1.21)
Subependymal hemorrhage	21/143 (15)	13/131 (10)		29/247 (12)	30/261 (11)	
Intraventricular hemorrhage	21/143 (15)	24/131 (18)		17/247 (7)	22/261 (8)	
Mild ventriculomegaly	0/143	0/131		2/247 (1)	4/261 (2)	
Intraventricular hemorrhage with ventricular dilatation	9/143 (6)	10/131 (8)		6/247 (2)	13/261 (5)	
Parenchymal hemorrhage	13/143 (9)	17/131 (13)		10/247 (4)	15/261 (6)	
Parenchymal cysts	1/143 (1)	2/131 (2)		2/247 (1)	3/261 (1)	
Intraventricular hemorrhage with dilatation or parenchymal hemorrhage	22/143 (15)	27/131 (21)		16/247 (6)	28/261 (11)	
Abnormality on late scan (>14 days)						
None	58/87 (67)	46/78 (59)	1.13 (0.89–1.43)	147/196 (75)	166/220 (75)	0.99 (0.89–1.11)
Mild ventriculomegaly	6/87 (7)	9/78 (12)		5/196 (3)	11/220 (5)	
Moderate or severe ventriculomegaly	5/87 (6)	4/78 (5)		8/196 (4)	5/220 (2)	
Periventricular leukomalacia	5/87 (6)	5/78 (6)		3/196 (2)	3/220 (1)	
Porencephaly	2/87 (2)	3/78 (4)		6/196 (3)	9/220 (4)	
Any major abnormality	12/87 (14)	12/78 (15)		17/196 (9)	17/220 (8)	

*Relative risks are for the infants receiving high-frequency oscillatory ventilation as compared with those receiving conventional ventilation. CI denotes confidence interval.

as soon as possible after birth. This feature makes it more difficult to compare the results of our study with those of others, since we included infants who would have been excluded from other studies because they required only minimal ventilation for a few hours. However, an analysis that excluded the 11 percent of infants who were extubated within the first 24 hours after birth (9 percent of those assigned to high-frequency oscillatory ventilation and 13 percent of those assigned to conventional ventilation) did not change our conclusions.

One of the criticisms of the original HIFI trial was that before the study, many of the participating units had virtually no experience with oscillation.[19] In our study, most participating centers had several years of experience using high-frequency oscillatory ventilation, and all had treated a minimum of 20 infants before the trial began. All centers in the United Kingdom were visited by trial personnel once every six months, and we provided a 24-hour telephone service to assist with problems related to the trial in order to maximize adherence to the protocol. Only two protocol violations were reported, and the infants in question were withdrawn from the study. The specified criteria for treatment failure were reached in a similar number of infants in the two groups.

The study may be criticized on the grounds that we did not specify a single type of ventilator or oscillator. In the laboratory, the three oscillators have similar characteristics in that volume delivery is impaired as the ventilator frequency is increased.[15,20] In practice, however, as Hatcher et al. point out,[20] the operator of the oscillator tries to achieve the desired effect by adjusting the mean airway pressure until the appropriate lung volume is achieved; thus, it could be argued that the measurement discrepancies observed among devices in laboratory tests are immaterial. Problems could arise if an infant were switched from one device to another[20]; in our study, only two infants were switched from the Dräger device to the SensorMedics device. We predicted that each oscillator would be used in equal numbers of infants in our study, but the SensorMedics 3100A was used in only 10 percent of infants. These infants had a higher rate of the primary outcome than those who underwent ventilation with the other devices, but since the choice of oscillator was not related to the condition of the infant at enrollment, these data are particularly difficult to interpret (see Supplementary Appendix 2, available with the full text of this article at http://www.nejm.org).

The Cochrane review[14] aroused concern about the risks of air leak and hemorrhagic brain lesions with high-frequency oscillatory ventilation. Our study did not substantiate this concern. Among the infants we studied, the frequencies of pneumothorax and pulmonary interstitial emphysema were similar in the two groups. The issue of brain injuries is less clear. In the original HIFI trial,[5] there were more grade 3 and grade 4 periventricular hemorrhages and periventricular leukomalacia in the infants who received high-frequency oscillatory ventilation. At follow-up, more of the children who had received high-frequency oscillatory ventilation had cerebral palsy. As our study began, a meta-analysis of other studies in which high-frequency ventilation was used with volume-recruitment strategies showed no significant association between high-frequency ventilation and intraventricular hemorrhage.[21] Subsequently, a further study showed an increased prevalence of severe intraventricular hemorrhage,[11] but after adjustment for base-line imbalances between groups, the difference was not significant. In our study, the prevalence of severe hemorrhagic brain lesions visible on ultrasonography was somewhat lower among infants who received high-frequency oscillatory ventilation than among those who received conventional ventilation. However, hemorrhagic brain lesions were a secondary outcome, and the critical threshold for statistical significance with the use of Bonferroni's correction ($P=0.004$) was not reached. The predictive value of ultrasonography for later developmental or neurologic disabilities may be relatively poor, and long-term follow-up will be needed.

We conclude that the results obtained with high-frequency oscillatory ventilation and conventional ventilation do not differ significantly in the early treatment of preterm infants with respiratory disease and that high-frequency oscillatory ventilation is not associated with a significant increase in the incidence of major cerebral lesions. Although there was no difference in the incidence of chronic lung disease, the effects of the two modes of ventilation on long-term respiratory and neurologic outcomes are not known.

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APPENDIX

In addition to the authors, the following persons participated in the United Kingdom Oscillation Study: *Study Team* — S. Hart, H. Beveridge, L. Gardiner, J. Rolfe, St. George's Hospital Medical School, London. *Steering Group* — F. Cockburn, Royal Hospital for Sick Children, Glasgow, United Kingdom; H. Halliday, Royal Maternity Hospital, Belfast, Northern Ireland; L. Davidson, National Perinatal Epidemiology Unit, Oxford, United Kingdom; S. Dart, Northern Ireland; M. Gill, Sussex, United Kingdom. *Data Monitoring Group* — P. Pharoah, University of Liverpool, Liverpool, United Kingdom; R. Lilford, Department of Health, Birmingham, United Kingdom; J. Stocks, R. Gilbert, Institute of Child Health, London. *Participating centers* — United Kingdom: Birmingham Heartlands Hospital, Birmingham; Chelsea and Westminster Hospital, London; Guy's and St. Thomas' Hospital, London; John Radcliffe Hospital, Oxford; Kings College Hospital, London; Lewisham Hospital, London; Medway Maritime Hospital, Kent; New Cross Hospital, Wolverhampton; Northampton General Hospital, Northampton; Northwick Park Hospital, London; Nottingham City Hospital, Nottingham; Queen Charlotte's Hospital, London; Queen's Medical Centre, Nottingham; Princess Anne Hospital, Southampton; Rosie Ma-

ternity Hospital, Cambridge; St. George's Hospital, London; St. Michael's Hospital, Bristol; St. Peter's Hospital, Chertsey; Simpson Memorial Hospital, Edinburgh; Singleton Hospital, Swansea; Southmead Hospital, Bristol; Ireland: Rotunda Hospital, Dublin; Australia: King George V Hospital, Sydney; Singapore: KK Women's and Children's Hospital.

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