

HIGH-FREQUENCY OSCILLATORY VENTILATION VERSUS CONVENTIONAL MECHANICAL VENTILATION FOR VERY-LOW-BIRTH-WEIGHT INFANTS

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ABSTRACT

Background The efficacy and safety of early high-frequency oscillatory ventilation as compared with conventional synchronized intermittent mandatory ventilation for the treatment of infants with very low birth weight have not been established.

Methods We conducted a randomized, multicenter clinical trial to determine whether infants treated with early high-frequency oscillatory ventilation were more likely than infants treated with synchronized intermittent mandatory ventilation to be alive without requiring supplemental oxygen at 36 weeks of postmenstrual age. Eligible infants weighed 601 to 1200 g at birth, were less than four hours of age, had received one dose of surfactant, and required ventilation with a mean airway pressure of at least 6 cm of water and a fraction of inspired oxygen of at least 0.25. Infants were stratified according to birth weight and exposure to prenatal corticosteroids and then randomly assigned to high-frequency oscillatory ventilation or synchronized intermittent mandatory ventilation. Ventilation was managed according to protocols designed to optimize lung inflation and blood gas values.

Results Five hundred infants were enrolled in the study. Infants randomly assigned to high-frequency oscillatory ventilation were successfully extubated earlier than infants assigned to synchronized intermittent mandatory ventilation ($P < 0.001$). Of infants assigned to high-frequency oscillatory ventilation, 56 percent were alive without a need for supplemental oxygen at 36 weeks of postmenstrual age, as compared with 47 percent of those receiving synchronized intermittent mandatory ventilation ($P = 0.046$). There was no difference between the groups in the risk of intracranial hemorrhage, cystic periventricular leukomalacia, or other complications.

Conclusions There was a small but significant benefit of high-frequency oscillatory ventilation in terms of the pulmonary outcome for very-low-birth-weight infants without an increase in the occurrence of other complications of premature birth. (N Engl J Med 2002; 347:643-52.)

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HIGH-FREQUENCY oscillatory ventilation delivers small tidal volumes generated by an oscillatory piston or diaphragm at rapid rates, superimposed on a variable mean airway pressure. Multiple studies in animals suggest advantages of high-frequency oscillatory venti-

lation as compared with conventional ventilation for supporting immature or injured lungs.¹⁻¹² However, clinical trials comparing high-frequency oscillatory ventilation with conventional ventilation in infants with very low birth weight have yielded mixed results.¹³⁻²⁵ These clinical trials varied widely in design, criteria for entry, the use or nonuse of exogenous surfactant, the strategy for lung recruitment (i.e., inflation), and the types of ventilators studied. Most compared high-frequency oscillatory ventilation with intermittent mandatory ventilation without tidal-volume monitoring. The potential role of high-frequency oscillatory ventilation in the care of very-low-birth-weight infants is further clouded by conflicting data suggesting that the use of such ventilation may be associated with an increased risk of intracranial hemorrhage or cystic periventricular leukomalacia.^{17,20,23} Thus, despite 20 years of experience with high-frequency oscillatory ventilation, there is no consensus about its role in the care of very-low-birth-weight infants.²⁶

We conducted an investigator-initiated, multicenter, randomized, noncrossover, controlled clinical trial comparing high-frequency oscillatory ventilation with synchronized intermittent mandatory ventilation with continuous tidal-volume monitoring to determine whether early institution of high-frequency oscillatory ventilation would improve the pulmonary outcome of very-low-birth-weight infants without increasing the incidence of intracranial hemorrhage or cystic periventricular leukomalacia.

METHODS

All aspects of study design, data collection and analysis, and presentation were under the control of the study's executive committee. Some equipment and funding were provided by industry sponsors, who were otherwise not involved with the protocol.

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Study Sites

The trial was conducted at 26 tertiary neonatal intensive care units, including community, university, and children's hospitals. Each site was visited by members of the executive committee before the study began. The institutional review board at each site approved the protocol, and written, informed parental consent was obtained for all enrolled infants.

Eligible Infants

Infants were eligible if they weighed 601 to 1200 g at birth, were appropriately developed for their gestational age, had received one dose of surfactant (Survanta, Ross Products Division, Abbott Laboratories), required conventional mechanical ventilation with a fraction of inspired oxygen (FiO_2) of at least 0.25 and a mean airway pressure of at least 6 cm of water, were less than 4 hours of age, and were expected to require mechanical ventilation for more than 24 hours. Infants were not eligible if they had a five-minute Apgar score of 3 or less, a base deficit of 15 or more before study entry, severe hypotension (a systolic blood pressure more than 2 SD below the mean for their birth weight²⁷ despite a total combined dose of dopamine, dobutamine, or both, of 20 μg per kilogram of body weight per minute), obvious chromosomal or congenital anomalies, congenital heart disease, or known neuromuscular disease.

Randomization

Infants were randomly assigned by members of the staff at the clinical coordinating center in Oakland, California, who could be contacted by pager 24 hours a day. Eligible infants were stratified according to birth weight (601 to 700, 701 to 800, 801 to 1000, and 1001 to 1200 g), exposure to antenatal corticosteroids, and study site. All infants received conventional ventilation before enrollment. Infants randomly assigned to high-frequency oscillatory ventilation were immediately switched to high-frequency oscillatory ventilation. Infants assigned to synchronized intermittent mandatory ventilation continued receiving synchronized intermittent mandatory ventilation or were switched to synchronized intermittent mandatory ventilation if necessary. Infants remained in the study until they were discharged from the hospital.

Ventilation Strategies

Infants assigned to high-frequency oscillatory ventilation received ventilation with the SensorMedics 3100A ventilator. Infants assigned to synchronized intermittent mandatory ventilation received ventilation with either the VIP Bird ventilator (Bird Products), the Babylog 8000 (North American Dräger), the Bear Cub Ventilator with attached Neonatal Volume Monitor, or the Bear Cub 750vs (Viasys Health Care). These ventilators provide flow-triggered synchronized intermittent mandatory ventilation and continuous tidal-volume monitoring at the hub (connection) of the endotracheal tube. For all infants assigned to synchronized intermittent mandatory ventilation, the assist sensitivity was set at 0.2 liter per minute; the VIP Bird termination-sensitivity option was not used.

The ventilation strategies and study protocol were tested and refined in a pilot study.²⁸ Strategies for ventilation for both groups emphasized lung recruitment (i.e., inflation) and avoidance of atelectasis and overdistention. We defined ideal lung inflation as expansion to 8 to 9.5 ribs for most infants (the top of the right hemidiaphragm relative to the posterior ribs on chest radiography at full inspiration), but 7 to 8 ribs for infants with air leak or chronic lung disease. For infants assigned to high-frequency oscillatory ventilation, the initial mean airway pressure was at least 2 cm of water higher than that received during conventional ventilation; the inspiratory:expiratory ratio was 0.33 and the frequency was 10 to 15 Hz. For infants assigned to synchronized intermittent mandatory ventilation, expiratory tidal volumes of 4 to 7 ml per kilogram of body weight were allowed, with a preferred target range of 5 to

6 ml per kilogram. The end expiratory pressure began at 4 to 6 cm of water, depending on the FiO_2 and lung inflation. Inspiratory times of 0.25 to 0.40 second were allowed, with rates not to exceed 60 breaths per minute.

The protocol dictated maintenance of arterial oxygen saturation, as measured by pulse oximetry, between 88 and 96 percent, an arterial pH of at least 7.20, and moderate permissive hypercapnia with a partial pressure of carbon dioxide (PCO_2) of 40 to 55 mm Hg. For infants with chronic lung disease, air-leak syndromes, or persistent hyperinflation, the target PCO_2 was 45 to 65 mm Hg.

The ventilation protocols included aggressive weaning if blood gases and lung inflation (as indicated by chest radiographs) remained within target ranges. At a minimum, assessments of blood gases were made 20 minutes after study entry, every 20 to 30 minutes until target ranges were achieved, then every 4 hours for 24 hours, every 6 hours from hours 25 to 72, and then daily until the infant was extubated and had not received nasal continuous positive airway pressure for three days. At a minimum, chest radiography was performed in infants assigned to high-frequency oscillatory ventilation at 1 to 2 hours, 4 to 6 hours, and 24 hours after study entry and then daily for 7 days or until extubation; for infants assigned to synchronized intermittent mandatory ventilation, radiographs were obtained daily for 3 days and then at 5 to 7 days if the infant was still receiving ventilation. Changes in ventilator settings were required if the criteria for target blood gas values and lung inflation were not met.²⁸ For infants receiving high-frequency oscillatory ventilation, these included an increased mean airway pressure for an FiO_2 greater than 0.40 and changes in amplitude to keep the PCO_2 within target ranges. For infants receiving synchronized intermittent mandatory ventilation, these included strict attention to expiratory tidal volume, with adjustments in end-expiratory pressure based on lung inflation and in rate based on the PCO_2 . For critically ill infants who could not be oxygenated or receive ventilation according to the protocol, clear exit criteria allowed treatment with alternative modes of ventilation. Such infants remained in the study and were analyzed according to their initial assignment. All other infants continued to receive ventilation according to their assigned mode until death or successful extubation.

Extubation was required when infants' condition had been stable for 6 to 12 hours while they were receiving minimal ventilatory support (for synchronized intermittent mandatory ventilation, the FiO_2 was no more than 0.25 and mean airway pressure was no more than 5 cm of water; for high-frequency oscillatory ventilation, the FiO_2 was no more than 0.25 and mean airway pressure was no more than 7 cm of water). The difference of 2 cm of water in mean airway pressure was intentional, since the flow characteristics of the SensorMedics ventilator at 33 percent inspiratory time result in an alveolar mean airway pressure 1 to 2 cm of water below that recorded at the hub of the endotracheal tube.^{29,30}

All infants were treated with caffeine or theophylline before extubation. When extubated, all infants were placed on nasal continuous positive airway pressure (Infant Flow, Electro Medical Equipment) and then weaned to a nasal cannula or room air. Infants for whom extubation failed because of inadequate oxygenation, inadequate ventilation, or severe apnea were placed back on their originally assigned ventilator.

Medical Treatment

All infants were treated with surfactant before study entry. Second and third doses were required if infants remained intubated with an FiO_2 of at least 0.30 6 to 12 hours after the previous dose. A fourth dose could be given at the discretion of the attending neonatologist. Surfactant was administered with use of in-line catheters (Trach Care Mac Multi-Access Catheter, Ballard Medical Products). Suctioning was performed only as needed, with the use of an in-line suction catheter (Trach Care Neonatal Closed Tracheal Suction System, Ballard Medical Products). Ventilation continued during the administration of surfactant and suctioning.

All infants received prophylactic indomethacin.³¹ Infants in whom patent ductus arteriosus subsequently developed were treated with additional indomethacin or surgical ligation.

Protocols delineated the use of dexamethasone, diuretics, and bronchodilators for the treatment of chronic lung disease. Infants who were more than 7 days of age and ventilated with an FiO_2 of at least 0.40 or who were more than 21 days of age and ventilated with an FiO_2 of at least 0.30 received dexamethasone (initial dose, 0.3 mg per kilogram per day, tapered over a period of 12 days). Infants who had completed a course of dexamethasone but who were still dependent on a ventilator with an FiO_2 of at least 0.30 were treated again with dexamethasone after a five-day hiatus. Infants more than 21 days old who were receiving dexamethasone and who were still ventilated with an FiO_2 greater than 0.40 were treated with diuretics. Bronchodilator therapy was allowed, but not required, for infants more than 14 days of age who were receiving dexamethasone and were ventilated with an FiO_2 greater than 0.40. Infants were screened for hearing loss at 34 to 36 weeks of postmenstrual age with the use of auditory brain-stem response testing (ALGO 2 or ALGO 2e, Natus Medical).

Respiratory Outcomes

The a priori primary null hypothesis was that there would be no difference between the two groups in the number of infants who were alive and did not require supplemental oxygen at 36 weeks of postmenstrual age. We carefully assessed the need for oxygen at 36 weeks by giving all infants still receiving oxygen a trial with room air. If at any time during the 24-hour evaluation period the infant required oxygen to maintain a partial oxygen saturation greater than 87 percent, the infant was considered to be dependent on oxygen. Successful extubation was defined a priori as occurring when an infant remained extubated for at least two weeks.

Assessment of Intracranial Hemorrhage, Cystic Periventricular Leukomalacia, and Other Clinical Outcomes

Cranial ultrasonography was performed between days 7 and 10, 21 and 30, and 50 and 60. Ultrasonograms were scored by both a radiologist at the site and the primary reviewer, who was unaware of the infant's study-group assignment, with the use of a standardized scoring sheet developed for the study. Intracranial hemorrhage was graded according to severity from I to IV, with higher numbers indicating more severe disease.³² The ultrasonographic evaluations were then reviewed by one of the principal investigators. Discrepancies in interpretation between the site radiologist and the masked reviewer were resolved by a second reviewer who was unaware of both the study-group assignment and the previous interpretations. Other outcomes were based on the diagnoses of the treating physicians.

Monitoring

Sites were monitored by means of site visits, weekly telephone calls, and reviews of the respiratory-care flow sheets from each study day. We calculated study compliance by dividing the time infants received ventilation into six-hour periods and assessing whether the ventilation protocols were followed during each of those periods.

Statistical Analysis

The study was based on the assumptions that 50 percent of the study population would be alive and not requiring supplemental oxygen at 36 weeks of postmenstrual age³³⁻³⁵ and that assignment to high-frequency oscillatory ventilation would result in a clinically important improvement in this outcome to 65 percent. Using a two-tailed alpha error of 0.05, a beta error of 0.10 (power of 90 percent), and — on the basis of the pilot study²⁸ — assuming a 6 percent rate of withdrawal and a 10 percent incidence of twins and triplets, we calculated the sample size to be 500.

Analyses were performed according to the intention-to-treat prin-

TABLE 1. CHARACTERISTICS OF INFANTS AT STUDY ENTRY.*

| CHARACTERISTIC | HIGH-FREQUENCY OSCILLATORY VENTILATION (N=244) | SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (N=254) | P VALUE |
|---|---|---|------------|
| Mean birth weight — g | 859±161 | 848±160 | 0.45 |
| Birth weight — no. (%) | | | |
| 601–700 g | 46 (19) | 55 (22) | 0.50 |
| 701–800 g | 57 (23) | 62 (24) | 0.83 |
| 801–1000 g | 87 (36) | 84 (33) | 0.57 |
| 1001–1200 g | 54 (22) | 53 (21) | 0.75 |
| Gestational age at birth — wk | 26.0±1.6 | 26.1±1.6 | 0.49 |
| Prenatal betamethasone therapy — no. (%)† | | | |
| Complete | 104 (43) | 108 (43) | 1.0 |
| Incomplete | 75 (31) | 72 (28) | 0.62 |
| Partial | 17 (7) | 25 (10) | 0.26 |
| None | 48 (20) | 49 (19) | 1.0 |
| Maternal chorioamnionitis — no. (%) | 28 (11) | 27 (11) | 0.78 |
| Mother positive for group B streptococcus — no. (%)‡ | 16 (7) | 24 (9) | 0.25 |
| Maternal toxemia — no. (%) | 30 (12) | 34 (13) | 0.79 |
| Maternal diabetes — no. (%) | 8 (3) | 9 (4) | 1.0 |
| Any prenatal care — no. (%) | 171 (70) | 168 (66) | 0.39 |
| Mother's race or ethnic group — no. (%)§ | | | |
| White | 128 (52) | 112 (44) | 0.07 |
| Black | 72 (30) | 92 (36) | 0.13 |
| Asian | 4 (2) | 9 (4) | 0.26 |
| Hispanic | 38 (16) | 38 (15) | 0.90 |
| Other or unknown | 2 (1) | 3 (1) | 1.0 |
| Maternal use of illicit drugs — no. (%)¶ | 13 (5) | 14 (5) | 1.0 |
| Delivery by cesarean section — no. (%) | 144 (59) | 150 (59) | 1.0 |
| Male sex — no. (%) | 127 (52) | 141 (55) | 0.47 |
| Singleton — no. (%) | 176 (72) | 195 (76) | 0.26 |
| Born in institution — no. (%) | 222 (91) | 231 (91) | 1.0 |
| Median Apgar score | | | |
| One-minute | 5 | 5 | 0.81 |
| Five-minute | 7 | 7 | 0.33 |
| Age at randomization — hr | 2.7±0.9 | 2.7±0.9 | 1.0 |
| Mean airway pressure — cm of water | 8.2±1.6 | 8.3±1.8 | 0.51 |
| FiO_2 | 0.57±0.25 | 0.60±0.27 | 0.20 |

*Plus-minus values are means ±SD. FiO_2 denotes fraction of inspired oxygen.

†A complete course of prenatal betamethasone was defined as two doses administered more than 24 hours but no more than 7 days before delivery; a partial course as one dose administered more than 24 hours but no more than 7 days before delivery; and incomplete as any steroids administered less than 24 hours or more than 7 days before delivery.

‡Treatment was at the discretion of the obstetrician.

§The mother's race or ethnic group was determined by the investigators, according to the medical record.

¶The use of illicit drugs was defined as exposure to heroin, methadone, cocaine, or amphetamines.

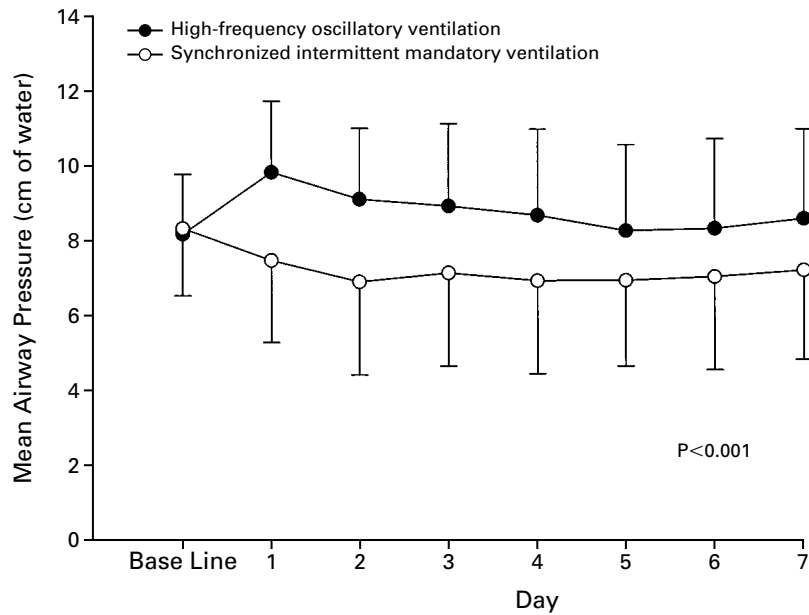


Figure 1. Mean (\pm SD) Airway Pressure during the First Seven Days of Life.

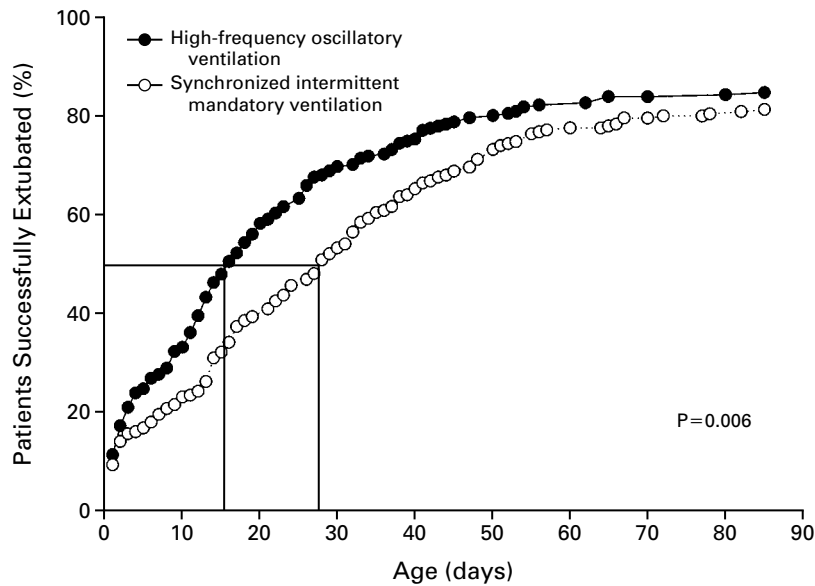


Figure 2. Kaplan–Meier Curves Showing Ages at Which Infants Were Successfully Extubated. The curves are significantly different ($P=0.006$ by the Cox proportional-hazards estimate; hazard ratio, 0.76 [95 percent confidence interval, 0.62 to 0.92]). The vertical lines show the age at which 50 percent of the infants assigned to each group were successfully extubated.

TABLE 2. RESPIRATORY OUTCOMES.

| OUTCOME | HIGH-FREQUENCY OSCILLATORY VENTILATION (N=244) | SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (N=254) | P VALUE |
|--|---|---|------------|
| At 36 weeks — no. with outcome/total no. (%)* | | | |
| Alive and weaned from all support | 131/234 (56) | 117/250 (47) | 0.046 |
| Birth weight | | | |
| 601–700 g | 12/44 (27) | 17/54 (31) | 0.67 |
| 701–800 g | 27/55 (49) | 21/60 (35) | 0.14 |
| 801–1000 g | 52/83 (63) | 45/84 (54) | 0.27 |
| 1001–1200 g | 40/52 (77) | 34/52 (65) | 0.28 |
| Death | 33/234 (14) | 40/250 (16) | 0.61 |
| Ventilation | 4/234 (2) | 12/250 (5) | 0.08 |
| Nasal continuous positive airway pressure | 2/234 (1) | 3/250 (1) | 1.0 |
| Supplemental oxygen | 64/234 (27) | 78/250 (31) | 0.37 |
| First extubation† | | | |
| Median age — days | 6 | 7 | 0.14 |
| Reintubation — no. of infants‡ | 99 | 115 | 0.21 |
| Reason for reintubation — no. of infants | | | |
| Apnea or bradycardia | 57 | 76 | 0.08 |
| Respiratory acidosis | 30 | 21 | 0.18 |
| Oxygenation | 7 | 10 | 0.62 |
| Other | 5 | 8 | 0.58 |
| Successful extubation† | | | |
| No. of infants | 200 | 204 | |
| Median age — days | 13 | 21 | <0.001 |
| Exited assigned mode of ventilation — no. of infants§ | | | |
| Total | 31 | 52 | 0.02 |
| Left at or before day 7 | 14 | 30 | 0.36 |
| Left per protocol | 23 | 38 | 1.0 |
| Changed to other study ventilator | 25 | 49 | 0.07 |

*Data were not available for patients withdrawn before 36 weeks of postmenstrual age.

†Data include some patients who underwent extubation before being withdrawn from the study.

‡Reintubation refers to a first reintubation only and does not include late reintubations for surgery.

§Data include only the first 28 days, since the protocol allowed some changes in the mode of ventilation after 28 days.

ciple, with all patients included who could be evaluated. Categorical outcomes were compared with use of Fisher's exact test. Normally distributed continuous outcomes were compared with use of the unpaired Student's t-test, and nonparametric continuous outcomes with use of the Wilcoxon rank-sum test or the Mann-Whitney U test. Serial data were compared with use of a repeated-measures analysis of variance. All analyses were conducted with two-tailed tests. Time-based analyses of age at extubation and age at the time the infant was weaned to room air are presented as Kaplan-Meier curves with Cox proportional-hazards estimates. The statistical software used included Instat (GraphPad Software) and SAS (SAS Institute).

RESULTS

Characteristics at Base Line

Between July 1998 and May 2000, 2226 infants who weighed 601 to 1200 g at birth were admitted to the study sites. Of these, 895 met the criteria for entry; 87 of these were not enrolled because of the unavailability of equipment, the parents of 158 refused consent, and no attempt was made to obtain consent for 150 infants. The remaining 500 infants were enrolled

(245 were assigned to high-frequency oscillatory ventilation and 255 to synchronized intermittent mandatory ventilation). Two infants with late-diagnosed congenital heart disease were subsequently excluded. Analyses were performed on the remaining 244 infants assigned to high-frequency oscillatory ventilation and the 254 assigned to synchronized intermittent mandatory ventilation. Fourteen infants (2.8 percent of the total study population of 500) were withdrawn by parental request (10 assigned to high-frequency oscillatory ventilation and 4 assigned to synchronized intermittent mandatory ventilation). Data on these infants were included in the analyses up to the time of their withdrawal. The characteristics of both groups at study entry are presented in Table 1.

Ventilatory Support

During the first seven days, infants assigned to high-frequency oscillatory ventilation, as expected, received ventilation with a higher mean airway pressure ($P <$

0.001) (Fig. 1). The mean FiO_2 was slightly higher in those assigned to high-frequency oscillatory ventilation (37 to 41 mm Hg, as compared with 30 to 36 mm Hg in those assigned to synchronized intermittent mandatory ventilation; $P=0.01$), but there was no significant difference between the groups in the mean partial oxygen saturation ($P=0.62$). Overall, the mean PCO_2 values were slightly lower in infants assigned to high-frequency oscillatory ventilation (43 to 48 mm Hg, as compared with 43 to 50 mm Hg in those assigned to synchronized intermittent mandatory ventilation; $P<0.001$); however, the PCO_2 remained within the target ranges in both treatment groups.

Outcome

As shown in Figure 2, the age at successful extubation was significantly lower for infants assigned to high-frequency oscillatory ventilation than for those assigned to synchronized intermittent mandatory ventilation ($P<0.001$). More infants assigned to high-frequency oscillatory ventilation were alive without requiring supplemental oxygen at 36 weeks of postmenstrual age (131 vs. 117 [56 percent vs. 47 percent]; relative risk, 1.2 [95 percent confidence interval, 1.0 to 1.5]; $P=0.046$) (Table 2). In addition to the status at 36 weeks, the a priori outcome for which

the statistical power of the study was designed, we evaluated the proportion of infants alive and not receiving any respiratory or oxygen support over time (Kaplan–Meier analysis) (Fig. 3). Major complications of prematurity are shown in Table 3. There were no significant differences in the incidence of intracranial hemorrhage, severe intracranial hemorrhage (grade III or IV), cystic periventricular leukomalacia, or combined severe intracranial hemorrhage and cystic periventricular leukomalacia. There were also no significant differences in the incidence of patent ductus arteriosus, pneumothorax, necrotizing enterocolitis, intestinal perforation, sepsis, retinopathy of prematurity, or hearing loss before discharge. Pulmonary hemorrhage was less likely to develop ($P=0.015$) and pulmonary interstitial emphysema was slightly more likely to develop in infants assigned to high-frequency oscillatory ventilation ($P=0.052$). Pulmonary interstitial emphysema and pulmonary hemorrhage were not prospectively defined, and these differences must be interpreted with caution.

Pharmacologic treatment in the two groups is shown in Table 4. Slightly more infants assigned to synchronized intermittent mandatory ventilation received only one dose of surfactant ($P=0.046$). Bronchodilators were used in fewer infants assigned to high-frequency oscillatory ventilation ($P=0.006$). The rate

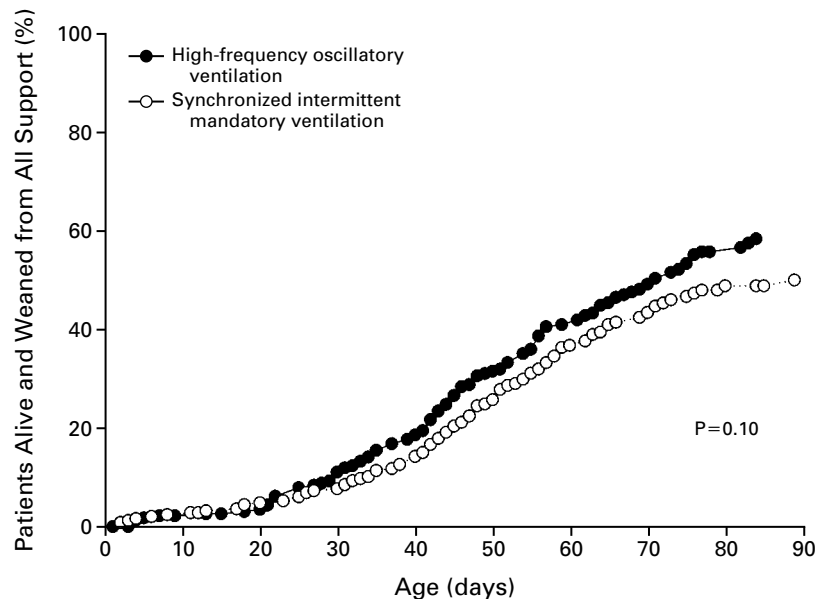


Figure 3. Kaplan–Meier Curves Showing Ages at Which Infants Were Successfully Weaned from All Support.

$P=0.10$ by the Cox proportional-hazards estimate; hazard ratio, 0.81 (95 percent confidence interval, 0.62 to 1.04).

TABLE 3. CLINICAL OUTCOMES.*

| OUTCOME | HIGH-FREQUENCY OSCILLATORY VENTILATION (N=244) | SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (N=254) | P VALUE |
|--|---|---|------------|
| | no./total no. (%) | | |
| Any intracranial hemorrhage | 113 (46) | 124 (49) | 0.59 |
| Severe intracranial hemorrhage (grade III or IV) | 45 (18) | 45 (18) | 0.91 |
| Cystic periventricular leukomalacia | 18 (7) | 26 (10) | 0.27 |
| Severe intracranial hemorrhage or cystic periventricular leukomalacia, according to birth weight | | | |
| 601–700 g | 9/46 (20) | 19/55 (35) | 0.12 |
| 701–800 g | 13/57 (23) | 18/62 (29) | 0.53 |
| 801–1000 g | 16/87 (18) | 14/84 (17) | 0.84 |
| 1001–1200 g | 12/54 (22) | 8/53 (15) | 0.46 |
| Total | 50 (20) | 59 (23) | 0.52 |
| Pneumothorax | 32 (13) | 33 (13) | 1.0 |
| Pulmonary interstitial emphysema | 48 (20) | 33 (13) | 0.05 |
| Pulmonary hemorrhage | 5 (2) | 17 (7) | 0.02 |
| Bacteremia or fungemia | 95 (39) | 108 (43) | 0.47 |
| Patent ductus arteriosus | 53 (22) | 67 (26) | 0.25 |
| Patent ductus arteriosus treated with ligation | 15 (6) | 22 (9) | 0.31 |
| Necrotizing enterocolitis | 31 (13) | 35 (14) | 0.79 |
| Isolated intestinal perforation | 12 (5) | 8 (3) | 0.37 |
| | mean ±SD | | |
| Age at first attempted oral feeding (days) | 7.2±5.9 | 7.6±7.7 | 0.52 |
| Age when last received parenteral nutrition (days) | 35.1±24.4 | 37.0±27.0 | 0.41 |
| Age at which birth weight was regained (days) | 11.5±7.8 | 10.9±7.6 | 0.39 |
| | no. (%) | | |
| Retinopathy of prematurity | | | |
| Stage 1 | 59 (24) | 53 (21) | 0.39 |
| Stage 2 | 52 (21) | 63 (25) | 0.40 |
| Stage 3 | 32 (13) | 41 (16) | 0.38 |
| Stage 4 | 2 (1) | 1 (1) | 0.62 |
| Surgery for retinopathy of prematurity | 30 (12) | 32 (13) | 1.0 |
| Hearing loss† | 29 (12) | 40 (16) | 0.24 |

*Data are included for all 498 patients up to the point at which they completed the study, died, or were withdrawn.

†Hearing loss was defined as a failed auditory brain-stem response test in at least one ear.

of compliance with the study protocol was 86 percent in infants assigned to high-frequency oscillatory ventilation and 87 percent in infants assigned to synchronized intermittent mandatory ventilation.

DISCUSSION

Infants treated with high-frequency oscillatory ventilation were successfully extubated earlier and were more likely than those treated with synchronized intermittent mandatory ventilation to be alive without requiring supplemental oxygen at 36 weeks of postmenstrual age. For every 11 infants treated with high-frequency oscillatory ventilation, 1 death or case of

chronic lung disease was prevented (absolute reduction in risk, 9.2 percent). These results confirm the findings of multiple studies in animals that have demonstrated the superiority of high-frequency oscillatory ventilation to conventional ventilation.¹⁻¹² They also confirm the results of Gerstmann et al. in a study of infants of higher birth weight.²¹

In 1989, the HIFI Study Group reported that high-frequency oscillatory ventilation failed to improve respiratory outcomes and perhaps increased the likelihood of severe intracranial hemorrhage and cystic periventricular leukomalacia.²⁰ Since that time, many changes have occurred in both neonatal care and ven-

TABLE 4. PHARMACOLOGIC TREATMENT.*

| TREATMENT | HIGH-FREQUENCY OSCILLATORY VENTILATION (N=244) | SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (N=254) | P VALUE |
|---|---|---|------------|
| | no. (%) | | |
| Surfactant doses required | | | |
| 1 | 70 (29) | 95 (37) | 0.046 |
| 2 | 72 (30) | 67 (26) | 0.48 |
| 3 | 68 (28) | 60 (24) | 0.31 |
| ≥4 | 34 (14) | 32 (13) | 0.69 |
| Pressors in first week | 115 (47) | 121 (48) | 0.93 |
| Inhaled bronchodilators | 80 (33) | 114 (45) | 0.006 |
| Diuretics | 112 (46) | 118 (46) | 0.93 |
| Systemic corticosteroids | | | |
| For hypotension | 5 (2) | 13 (5) | 0.09 |
| For chronic lung disease according to protocol | 112 (46) | 139 (55) | 0.06 |
| For other indication | 41 (17) | 53 (21) | 0.26 |
| For any indication† | 135 (55) | 159 (63) | 0.10 |
| | mean ±SD | | |
| Days receiving systemic corticosteroids‡ | 17.2±11.9 | 20.0±13.2 | 0.06 |

*Data are included for all 498 patients up to the point at which they completed the study, died, or were withdrawn.

†Some patients received corticosteroids for more than one indication.

‡Values indicate the number of days per patient treated.

tilation strategies. Surfactant replacement has become a routine treatment, and more is known about the importance of optimal lung recruitment during high-frequency ventilation^{4,36-41} and about the importance of monitoring and controlling tidal volume during conventional ventilation.⁴²⁻⁴⁵ The smaller trials of high-frequency ventilation that followed the HIFI study yielded conflicting results. These trials varied widely in criteria for entry and methods.^{13-19,21-25} Some studies were undertaken before the introduction of surfactant-replacement therapy^{17,19} or employed high-frequency devices not currently used in the United States.^{22,23} Other trials did not consistently use a lung-recruitment strategy¹⁶ or studied relatively mature preterm infants.²¹ Most studies compared high-frequency ventilation with nonsynchronized intermittent mandatory ventilation.^{17-19,21,22,24,25}

We designed this trial to compare high-frequency oscillatory ventilation with a type of synchronized intermittent mandatory ventilation in which both breath-triggering and tidal-volume monitoring occurred at the airway.⁴⁶ We chose to compare high-frequency oscillatory ventilation with synchronized intermittent mandatory ventilation because several studies suggest improved pulmonary outcomes with synchronized intermittent mandatory ventilation as

compared with nonsynchronized ventilator breathing.^{44,47-51} We chose a narrow range of tidal volumes on the basis of data from studies in both animals and humans, which suggested that lower tidal volumes decrease volutrauma.^{42,43,52} Our management protocols for high-frequency oscillatory ventilation and synchronized intermittent mandatory ventilation were designed to optimize lung recruitment and avoid maneuvers that could lead to derecruitment. Lung recruitment has been demonstrated to be important for optimal outcome with high-frequency oscillatory ventilation.^{4,7,9,36-38,40,41} Given that the FiO₂ was slightly higher in the infants assigned to high-frequency oscillatory ventilation during the first week, it is possible that even better recruitment could have been accomplished.⁵³ Nonetheless, we found that high-frequency oscillatory ventilation used with this strategy significantly improved respiratory outcome in this population.

Although the HIFI trial suggested that high-frequency oscillatory ventilation increased the incidence of intracranial hemorrhage and cystic periventricular leukomalacia,²⁰ other studies have yielded conflicting results.^{17,19,21,23} Our large study found no difference in the incidence of intracranial hemorrhage or cystic periventricular leukomalacia, findings consistent with the results of a prior meta-analysis.⁵³ The incidence of severe intracranial hemorrhage in our study was similar to that seen in other studies.^{54,55} The incidence of cystic periventricular leukomalacia in both the infants assigned to high-frequency oscillatory ventilation and those assigned to synchronized intermittent mandatory ventilation was higher than some published rates,⁵⁶ probably because cystic periventricular leukomalacia may be missed if cranial ultrasonography is not performed six to eight weeks after birth.⁵⁷⁻⁵⁹ Half of the cases of cystic periventricular leukomalacia in our study subjects were diagnosed at the time of the third cranial ultrasound examination.

We believe that the marked decrease in the number of days before successful extubation and the increase in the number of infants who survived without chronic lung disease in the group assigned to high-frequency oscillatory ventilation suggest that high-frequency oscillatory ventilation offers a small but significant benefit at experienced centers and, in such settings, should be considered the first line of ventilatory support in this group of very preterm infants.

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APPENDIX

Members of the executive committee were S.E. Courtney, D.J. Durand, and J.M. Asselin. The following institutions and investigators participated in the Neonatal Ventilation Study Group: *Albany Medical Center, Albany, N.Y.* — M. Fisher, P. Graziano, and S. Boynton; *Children's Hospital Oakland, Oakland, Calif.* — L. Jurcisin; *Children's Hospital of Orange County, Orange, Calif.* — J. Cleary and E. Drake; *City Avenue Hospital, Philadelphia* — K. Solarin, D. Miller, and S. Vagelaras; *Cooper Hospital—University Medical Center, Camden, N.J.* — J. Saslow and J. Hart; *Crouse Hospital, Syracuse, N.Y.* — T. Curran and P. Parker; *Geisinger Medical Center, Danville, Pa.* — J. Cook and J. Conrad; *Louisiana State University Medical Center, Shreveport* — A. Pramanik and J. Loggins; *Kosair Children's Hospital, University of Louisville School of Medicine, Louisville, Ky.* — D.L. Stewart and A. Hilbert; *MeritCare Medical Center, Fargo, N.D.* — V. Fearing; *New Hanover Regional Medical Center, Wilmington, N.C.* — R. McArthur, S. Schariat, B. Justason, and J. Check; *Ochsner Foundation Hospital, New Orleans* — H. Ginsberg, W. Quinn, and L. Kimble; *Saint Francis Medical Center, Monroe, La.* — M. deSolar, D. Wood, and M. Wooten; *Saint Joseph's Hospital, Phoenix, Ariz.* — M. Hart and E. Ranthum; *Parkview Memorial Hospital, Fort Wayne, Ind.* — I. Bilyk and C. Quackenbush; *Schneider Children's Hospital, Long Island Jewish Medical Center, New Hyde Park, N.Y.* — A. Steele and B. Wilkens; *Spartanburg Regional Medical Center, Spartanburg, S.C.* — V. Iskersky and B. McKown; *University of California at Irvine, Irvine* — B. Govindaswami, C. Uy, J. Denson, and S. Kusano; *University of Connecticut Health Center, Farmington* — M. Pappagalio, M. Holman, R. Arens, and K. Jennings; *University Medical Center at Stony Brook, Stony Brook, N.Y.* and *Westchester Medical Center, Valhalla, N.Y.* — L. Parton, A. Rohan, and N. Dweck; *Wake Forest University School of Medicine (North Carolina Baptist Medical Center and Forsyth Medical Center), Winston-Salem, N.C.* — M. Fuloria and B.J. Hansell; *Women's and Children's Hospital and the Hospital of the Good Samaritan, Los Angeles* — R. Ramanathan, R. Erickson, H. Chinchilla, and K. Scott; *Shands Jacksonville, Wolfson Children's Hospital, and the University of Florida Health Science Center, Jacksonville* — E. Case and A. Kellum.

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