Prospective Randomized Multicenter Comparison of High-Frequency Oscillatory Ventilation and Conventional Ventilation in Preterm Infants of Less Than 30 Weeks With Respiratory Distress Syndrome

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ABSTRACT. *Background.* **Early use of high-frequency ventilation and exogenous surfactant is proposed as the optimal mode of ventilatory support in infants with respiratory distress syndrome. In very premature infants, we tested the hypothesis that high-frequency versus conventional ventilation could decrease exogenous surfactant requirements and improve pulmonary outcome, without altering the complication rate, including that of severe intraventricular hemorrhage.**

Methods. **Preterm infants with a postmenstrual age of 24 to 29 weeks, presenting with respiratory distress syndrome were randomly assigned to high-frequency oscillatory ventilation (lung volume recruitment strategy) or conventional ventilation.**

Results. **Two hundred seventy-three infants were enrolled. One hundred fifty-three had a postmenstrual age of 24 to 27 weeks, and 143 had a birth weight ≤1000 g. One hundred thirty-four infants were randomized at 142 minutes of life (median) to receive conventional ventilation (mean postmenstrual age at birth: 27. 6 ± 1.5 weeks; mean birth weight: 997 ± 245 g); and 139 infants were randomized at 145 minutes of life to receive high-frequency ventilation (mean postmenstrual age at birth: 27.5 ± 1.4 weeks; mean birth weight: 976 ± 219 g).**

High-frequency ventilation, compared with conventional ventilation, was associated with a twofold reduction in the requirement for ≥2 instillations of exogenous surfactant (30% vs 62%; odds ratio: .27; 95% confidence interval: .16–.44) and no difference in pulmonary outcome. The incidence of severe intraventricular hemorrhage was 24% in the high-frequency group and 14% in the conventional ventilation group (adjusted odds ratio: 1.50; 95% confidence interval: .68–3.30).

Conclusion. **Early use of high-frequency oscillatory ventilation in very premature infants decreases exogenous surfactant requirements, does not improve the pulmonary outcome, and may be associated with an increased incidence of severe intraventricular hemorrhage.** *Pediatrics* **2001;107:363–372;** ***prematurity, high-frequency ventilation, chronic lung disease, multicenter trial, intraventricular hemorrhage.***

ABBREVIATIONS. Po_2, partial pressure of oxygen; FIo_2, fraction of inspired oxygen; Pco_2, partial pressure of carbon dioxide; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Increasing survival rates of very premature infants are associated with a high incidence of chronic lung disease, in which volutrauma is believed to play an important role. The objective of the various high-frequency ventilation techniques is to reduce acute lung injury. In animals, the pulmonary benefits of high-frequency ventilation versus conventional ventilation have been demonstrated without exogenous surfactant[1] and in combination with this treatment in some,[2–5] but not all experiments. In infants, the message from neonatal trials remains unclear,[6–12] resulting in an ongoing debate concerning the best ventilation mode for the management of respiratory distress syndrome. Because of the wider use of antenatal steroids and exogenous surfactant over recent years, new studies are required. We tested the hypothesis that, in infants born before 30 weeks, early use of high-frequency oscillatory ventilation with a lung volume recruitment strategy can decrease the exogenous surfactant requirements and improve pulmonary outcome, without altering the incidence of severe intraventricular hemorrhage.

METHODS

Study Organization and Patient Selection

Twelve centers initially agreed to participate in this study, but 2 of these 12 centers subsequently withdrew from the study after the inclusion of 4 patients (Fig 1). One center could unexpectedly not obtain a second oscillator, although the protocol required that at least 2 oscillators be available in each center. The second center, which had a 10-year experience of high-frequency oscillatory ventilation, withdrew because of the excessive reluctance of the team to accept randomization and the resulting use of conventional ventilation in half of the patients.

The study protocol and the consent form were approved by the appropriate ethics committees. French national regulations require written consent from both parents after they have been given detailed medical explanations, including the fact that they can deny consent without any consequences for the quality of care of their infant. Because these conditions cannot be adequately met in the emergency context of neonatal intensive care, an emergency procedure was authorized by the ethics committee, allowing ran-

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Received for publication Jun 2, 2000; accepted Sep 18, 2000.

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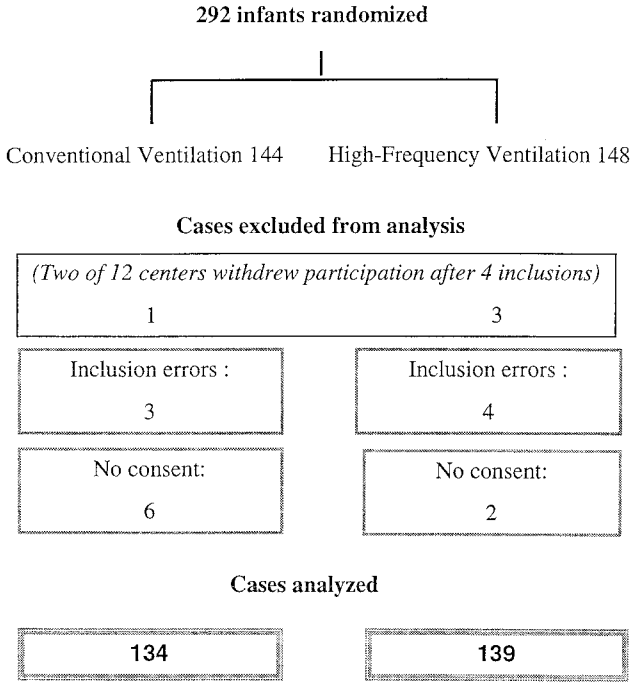

Fig 1. Recruitment.

domization before obtaining the parents' consent. Consent was requested as soon as possible after birth, sometimes after randomization. When it was not obtained, the corresponding cases were excluded from the analysis (Fig 1).

Infants were eligible when their postmenstrual age at birth was between 24 weeks and 29 weeks, when they required mechanical ventilation before 6 hours of life, and when they presented a partial pressure of oxygen (Po_2):fraction of inspired oxygen (FIo_2) ratio <200, and radiograph criteria of respiratory distress syndrome. To determine the Po_2:FIo_2 ratio, at the time of randomization and throughout the study, the Po_2 value was obtained in a quiet state from an arterial blood sample or by transcutaneous measurement. Infants were not eligible when grade 3 or 4 intraventricular hemorrhage or pulmonary air leak was diagnosed before randomization or in the case of rupture of membranes before 24 weeks of gestation or severe malformations or hydrops.

A review board regularly reviewed trial data for beneficial or adverse effects and made recommendations about whether enrolment should be continued.

Randomization and Endpoints

Eligible patients were assigned to 1 of the 2 treatments based on a computer-generated randomization plan. Randomization, which was stratified by center and postmenstrual age (24–27 and 28–29 weeks), was performed at the coordinating center, after telephone calls, using separate sets of sealed envelopes. A balanced block randomization plan was used to have similar numbers of patients in each treatment group and each of the 2 strata.

The primary endpoints were the need for repeated instillations of exogenous surfactant, after a first instillation to all patients, and survival without supplemental oxygen at 28 days of age. Secondary endpoints were the incidence of chronic lung disease at 36 weeks of postmenstrual age, air leak, and severe intraventricular hemorrhage.

Treatment Strategies

To obtain maximum uniformity of definitions and decisions, investigators participated in design of the protocol.

Use of Ventilators

Ventilator strategies and equipment were similar in all centers, and all teams had extensive experience with ventilatory assistance, including high-frequency oscillatory ventilation. Use of the Babylog 8000 (Drägerwerk, Lübeck, Germany) and the synchronized ventilation mode was recommended for conventional ventilation. Inspiratory time was set at <.45 second. Peak inspiratory pressure was set at the lowest level compatible with maintaining the partial pressure of carbon dioxide (Pco_2) level within target values. The same piston oscillator (OHF1; Dufour, Villeneuve d'Ascq, France), was used in all centers. The inspiratory-to-expiratory ratio was 1:1. The frequency was set at 15 Hz.[13] Peak-to-peak pressure was set according to the Pco_2 level.

The infants were placed on conventional ventilation for the shortest possible time required to assess inclusion criteria. After randomization, infants of the corresponding group were immediately switched to high-frequency ventilation.

Lung Volume Recruitment Strategy

The procedure for lung volume recruitment in the high-frequency oscillation group is described on Fig 2. Initial mean airway pressure was set at 14 cm H_2O when FIo_2 was >.4, and 2 cm H_2O higher than with conventional ventilation when FIo_2 was ≤.4. Further optimization of lung volume was performed by testing the effects of a series of 3 or 4 short consecutive sighs lasting <1 second, with a pressure set at 4 cm H_2O above mean airway pressure. Improvement in oxygenation after sighs was considered an indication to increase mean airway pressure by 2 cm H_2O. When FIo_2 was >.4, mean airway pressure was increased accordingly from 14 to 16 cm H_2O when oxygenation improved after sighs, and the effect of sighs was rechecked after stabilization of oxygenation. Mean airway pressure was increased to 18 cm H_2O when oxygenation was further improved. Testing the effect of higher pressure was not recommended in the protocol but was allowed when considered necessary by the neonatologist in charge. When FIo_2 was ≤.4, the effect of sighs was tested only once, and mean airway pressure was set 2 cm H_2O higher than before when oxygenation was improved.

Similar efforts to recruit lung volume were not performed in the conventional ventilation group, in contrast with the high-frequency arm. In agreement with the procedures used in the various centers, positive end expiratory pressure was set at 4 or 5 cm H_2O, according to oxygen requirement and the degree of lung inflation on chest radiographs.

Exogenous Surfactant

After randomization, a first dose of exogenous surfactant (Curosurf: 200 mg/kg) was given to all infants in the 2 groups. In the

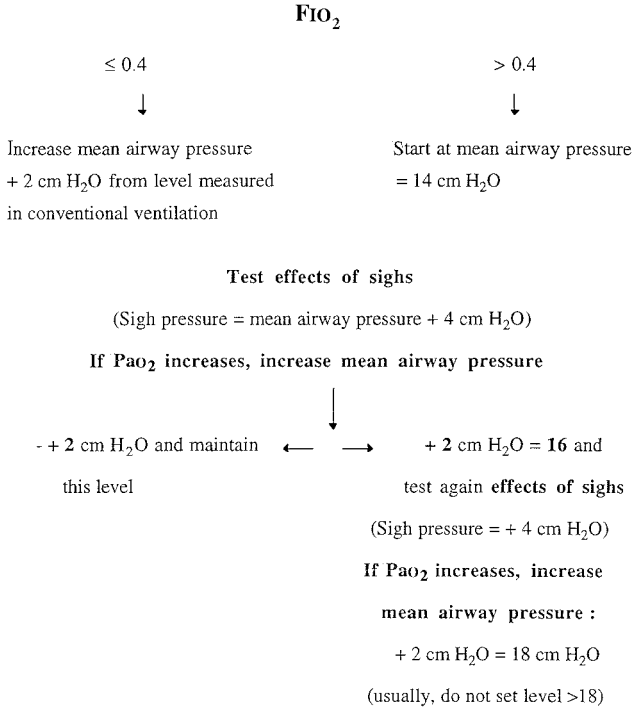

Fig 2. Optimization of lung volume after switch from conventional to high-frequency ventilation in the high-frequency group.

high-frequency group, exogenous surfactant was given after lung volume recruitment. Up to 2 more doses (Curosurf: 100 mg/kg) were allowed when Po_2:FIo_2 was <200. The usual interval between instillations was 12 hours but could be shorter in severe cases (see below).

Ventilatory Care

Target values for Pco_2, Pao_2, or transcutaneous Po_2, and oxygen hemoglobin saturation during the first few days were: 40 to 50 mm Hg, 50 to 70 mm Hg, and 90% to 95%, respectively. At predetermined intervals and before any treatment change, ventilation parameters were recorded, blood gases were measured and Po_2:FIo_2 ratio was calculated. During the first 10 days of life, the same mode of respiratory support was maintained until weaning, and, in case of weaning failure, whenever possible (ie, when an oscillator was still available). In the conventional ventilation group, peak pressure was decreased first. Positive end expiratory pressure was decreased to 3 cm H_2O when oxygen requirement was <.3 and was maintained above 2 cm H_2O for 24 hours after the first exogenous surfactant instillation, when overinflation was not observed on chest radiographs. Overinflation was defined as a flattened diaphragm at or below the ninth posterior rib. In the high-frequency group, overinflation was avoided by testing the tolerance of decreasing mean airway pressure by 2 cm H_2O steps when it was >14 cm H_2O, and by 1 cm H_2O steps when mean airway pressure was ≤14 cm H_2O. When oxygenation deteriorated after a pressure decrease, mean airway pressure was reset to the previous level. Assessments of the adequacy of mean airway pressure setting were repeated every 30 minutes during the 2 hours after instillation of Curosurf; and at least every 2 hours thereafter. Chest radiographs showing overinflation also constituted an indication to decrease mean airway pressure.

The following objective criteria were used to decide on extubation in clinically stable infants requiring oxygen concentrations <.30: 1) in the conventional ventilation group, a ventilatory rate <20 per minute and peak pressure <15 cm H_2O; 2) in the high-frequency group, mean airway pressure <8 cm H_2O and peak-to-peak pressure <35 cm H_2O.

Changes in Treatment

During the 10-day period, switching from one ventilation technique to the other or the use of nitric oxide or corticosteroids were only permitted when preestablished ventilatory and/or radiographic treatment failure criteria were met. The choice between these 3 options was left to the discretion of the team in charge. 1) Ventilatory treatment failure criteria: after exogenous surfactant instillations, oxygen concentration requirements >.5 and/or peak pressure >25 cm H_2O in the conventional group or a mean airway pressure >14 cm H_2O in the high-frequency group. When ventilatory treatment failure criteria were met within 12 hours after exogenous surfactant instillation, the second or third instillation was performed. Treatment could be changed thereafter. 2) Radiographic treatment failure criteria: development of air leak, which was defined as the occurrence of pneumothorax or pulmonary interstitial emphysema. Chest radiographs showing the development of air leak were reviewed at the coordinating center (see below). When infants were switched to the alternative ventilator, all analyses were conducted according to the infant's original group assignment.

Perinatal Data and General Infant Care

Relevant perinatal characteristics were recorded prospectively, to detect possible confounding factors.

Chest radiographs were performed at least once a day until day 3, and every other day from days 4 to 9. Chest radiographs performed at 28 days of age were interpreted for the presence or absence of bronchopulmonary dysplasia in each center and were reviewed thereafter by a pediatric radiologist (C.A.) not informed about the group assignment, using the radiographic scoring system proposed by Edwards.[14] Supplemental oxygen was considered to be required when supplemental oxygen had to be used to maintain oxygen saturation (pulse oxymetry) above 90%.

Cranial ultrasound examinations were performed before randomization whenever possible, during the first week at the discretion of each team, and between days 7 and 10 and at day 28. To obtain uniformity of intraventricular hemorrhage grading, all ultrasound examinations indicating the presence of grade 2, 3, or 4 intraventricular hemorrhage were reviewed at the coordinating center by a radiologist (C.A.) not informed about the group assignment. The results reported in this article are those of this reviewed grading. Cranial ultrasound examination was not performed before randomization in some of the infants included. To be able to attribute the development of intraventricular to each ventilatory strategy, a separate analysis was, therefore, performed on those cases in which it was possible to demonstrate that grade 3 or 4 intraventricular hemorrhage occurred after randomization (see "Discussion").

Diagnosis of necrotizing enterocolitis was based on the usual criteria: bloody stools and pneumatosis intestinalis on abdominal radiograph.

Outcome

The infant's clinical condition was assessed at 10 days, 28 days, and 36 and 42 weeks of postmenstrual age.

Sample Size, Data Analysis, and Monitoring

Data from the coordinating center concerning infants with a gestational age <30 weeks were used to calculate the sample size, based on the 2 primary endpoints, with a probability of type 1 error (α level) of .05, and a power of 80%. The sample size was calculated to detect a twofold reduction of exogenous surfactant reinstillation, from 20% to 10%. After inclusion of 160 patients, the global reinstillation rate was found to be 40% instead of the predicted 20%. Based on the observed reinstillation rate, the investigators' committee decided to decrease the initial calculated sample of 200 infants per group to 100 infants per group. A sample of 100 patients per group would be necessary to detect an increase from 45% to 65% in survival without supplemental oxygen at 28 days of age. A sample size of 250 patients was, therefore, deemed necessary to address our 2 primary endpoints, taking into account the uncertainty concerning final surfactant reinstillation rates. Data analysis was performed using SAS software (SAS, Cary, NC). To assess the effect of high-frequency oscillatory ventilation, crude and adjusted odds ratios (ORs) are presented with corresponding 95% confidence intervals (CIs). The adjusted ORs were computed by a multiple logistic regression. The factors included were either perinatal characteristics usually considered to be related to the development of intraventricular hemorrhage or 2 factors that were unevenly distributed in the 2 groups (presence or absence of high blood pressure during pregnancy and 5-minute Apgar score ≤6 or ≥7; see "Results" section and Tables).

RESULTS

Recruitment

Two hundred ninety-two infants were randomized between November 15, 1996 and June 30, 1998. Distribution of the infants between the 2 groups, exclusions, and the final number of cases for analysis are shown on Fig 1.

Comparability of Treatment Groups (Table 1)

Comparability of the 2 treatment groups was assessed for several characteristics, some of which are listed in Table 1. Other characteristics, not shown in Table 1 were: abruptio placentae, diabetes, prolonged rupture of membranes, fetal distress, use of β mimetics, and intrauterine growth retardation. There was no difference between the 2 groups for most of these characteristics. However, compared with the high-frequency group, the conventional group presented a higher frequency of preeclampsia and high blood pressure during pregnancy and the 5-minute Apgar score was more frequently ≥7 (Table 1).

Compliance With the Protocol

Timing of randomization, time to switch to the oscillator, and use of the lung volume recruitment

TABLE 1. Patients

Perinatal Characteristics	Conventional (n = 134)	High-Frequency (n = 139)
Maternal	*n* (%)	*n* (%)
Preeclampsia	26 (19)	12 (9)
High blood pressure	42 (31)	26 (19)
Multiple pregnancy	37 (28)	44 (32)
Antenatal steroids	74 (55)	72 (52)
Cesarean section	76 (57)	71 (51)
African or Caribbean origin	18 (13)	16 (12)
Neonatal	Mean (SD)	Mean (SD)
Birth weight (g)	997 (245)	976 (219)
Postmenstrual age (wk)	27.6 (1.5)	27.5 (1.4)
	n (%)	*n* (%)
Birth weight ≤1000 g	64 (48)	79 (57)
Postmenstrual age 24–27 wk	72 (54)	81 (58)
Born in the center	92 (69)	99 (71)
5-min Apgar score ≥7*	101/118 (86)	88/120 (73)
Males	77 (57)	82 (59)
Timing in min	Median (interquartile)	Median (interquartile)
Age at randomization	142 (118)	145 (95)
Delay randomization to high-frequency		15 (20)
Delay randomization to surfactant n° 1	25 (32)	45 (50)
Respiratory data	Median (interquartile)	Median (interquartile)
Before randomization		
Po_2:Fio_2	87 (63)	91 (70)
Mean airway pressure (cm H_2O)	10 (3)	10 (2)
Before second surfactant instillation		
Po_2:Fio_2	130 (65)	125 (71)

* Missing values.

strategy (see below) in the high-frequency group, use of exogenous surfactant based on Po_2:Fio_2 ratio <200 both for inclusion and for subsequent instillations, treatment changes (see below), and extubation trials were performed in agreement with the protocol (Tables 1 and 2). The recommended preference for using the Babylog 8000 in the conventional ventilation group was followed in 118 of 154 cases.

Primary Endpoints (Table 2)

Twice as many infants in the conventional group required ≥2 instillations of exogenous surfactant than in the high-frequency group. This difference was significant.

A similar proportion of infants survived without supplemental oxygen at 28 days of age in the 2 groups.

Secondary Endpoints (Table 2)

A similar incidence of air leak was observed after randomization in the 2 groups.

After adjustment, the difference in the incidence of chronic lung disease at 36 weeks between the 2 groups is close to statistical significance (P = .09).

Considering both survivors and nonsurvivors, fewer cases of grade 3 or 4 intraventricular hemorrhage were observed in the conventional group than in the high-frequency group. The crude difference

TABLE 2. Endpoints

	Conventional (n = 134) *n* (%)	High-Frequency (n = 139) *n* (%)	OR [95% CI]	Adjusted OR [95% CI]*
Primary endpoints				
Requirement of ≥2 instillations of surfactant	83 (62)	42 (30)	.27 [.16–.44]	.20 [.11–.38]
Survival without oxygen requirement at 28 d†	60 (55)	60 (54)	.98 [.58–1.67]	.93 [.49–1.78]
Secondary endpoints				
Air leak incidence after randomization				
Pulmonary interstitial Emphysema	15 (11)	15 (11)	.96 [.45–2.05]	1.11 [.43–2.86]
Pneumothorax	4 (3)	7 (5)	1.72 [.50–5.96]	.98 [.18–5.21]
Supplemental oxygen at 36 wk‡	30 (28)	24 (22)	.73 [.39–1.36]	.53 [.24–1.14]
Incidence of intraventricular hemorrhage grades 3–4	19 (14)	34 (24)	1.94 [1.05–3.60]	1.50 [.68–3.30]

* Adjustment on: mode of ventilation, blood pressure high or not high during pregnancy, Apgar score ≤6 or ≥7 at 5 minutes, birth weight ≤1000 and >1000 g, postmenstrual age <28 weeks and ≥28 weeks, inborn or outborn, use or no use of antenatal steroids, and Po_2:Fio_2 <100 or ≥100.
† Calculated in survivors at 28 days (n = 110 and n = 111).
‡ Calculated in survivors at 36 weeks (n = 107 and n = 108).

was significant but was no longer significant when considering the adjusted OR. This was because of high blood pressure during pregnancy, which was more frequent in the conventional group and was negatively associated with intraventricular hemorrhage. The possible confounding effect of cases switched from one ventilatory mode to the other was also assessed. Grade 3 or 4 intraventricular hemorrhage was observed in 9 of 95 infants (9.5%) who received conventional ventilation only, versus 44 of 177 infants (24.9%) who received high-frequency ventilation after randomization or who were switched from conventional ventilation (OR: 3.16; 95% CI: 1.51–6.63; $P = .002$).

Clinical Course and Outcome

Respiratory Outcome

Day 0 to day 9 (ventilation parameters): mean airway pressure and inspired oxygen concentration values before randomization and during the first 48 hours are shown in Figs 3 and 4.

Pco_2 before randomization was not significantly different between the conventional and high-frequency groups. After randomization and switch to high-frequency in the corresponding arm and before instillation of exogenous surfactant, Pco_2 was higher (43 mm Hg [14]) in the conventional group than in the high-frequency group (39 mm Hg [12]; median and interquartile; $P = .004$). A significant difference was observed for up to 12 hours after randomization, and the greatest difference was observed 6 hours after randomization (39 mm Hg [12] vs 35 mm Hg [8.5]; $P = .0001$).

Day 0 to day 9 (treatment changes; Table 3): no significant difference in the frequency of treatment changes was observed between the 2 groups. However, switching from conventional to high-frequency was significantly more frequent than switching from high-frequency to conventional.

Day 0 to day 9 (weaning; Table 3): extubation was attempted more frequently in infants in the high-frequency group than in the conventional group, but weaning also failed more frequently.

From day 10 to 42 weeks of postmenstrual age, no difference was observed between the 2 groups for the parameters listed in Table 4.

General Outcome

The rates of the various complications listed in Table 5 were similar in the 2 groups. Grade 3 retinopathy of prematurity occurred in 8/21 cases (38%) in the conventional and 6/20 cases (30%) in the high-frequency group (not significant); and there was no grade 4 retinopathy. There was no difference in use of sedation (data not shown).

Results observed in the 2 postmenstrual age strata are shown in Table 6. The most immature infants required more instillations of exogenous surfactant, but the significant difference between the 2 modes of ventilation was still observed.

DISCUSSION

In this trial, the use of high-frequency oscillatory ventilation with a lung volume recruitment strategy was associated with a decrease in exogenous surfactant requirements and did not modify pulmonary outcome but was associated with an increased incidence of severe intraventricular hemorrhages, which was not significant when considering the adjusted OR.

Exogenous surfactant is the undisputed first-line treatment of respiratory distress syndrome and was, therefore, administered once to each infant. An early rescue approach was adopted, based on a Po_2:Fio_2

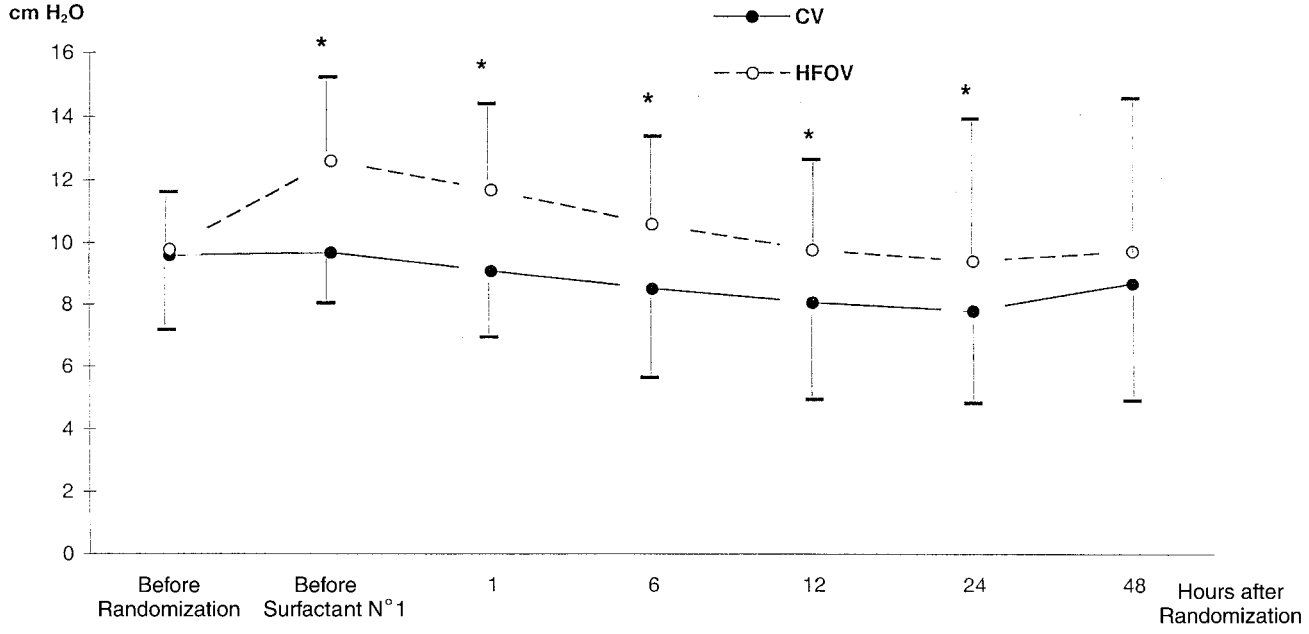

Fig 3. Mean values and standard deviation (SD) for mean airway pressure from inclusion to 48 hours of life. The asterisk indicates significant differences ($P < .001$).

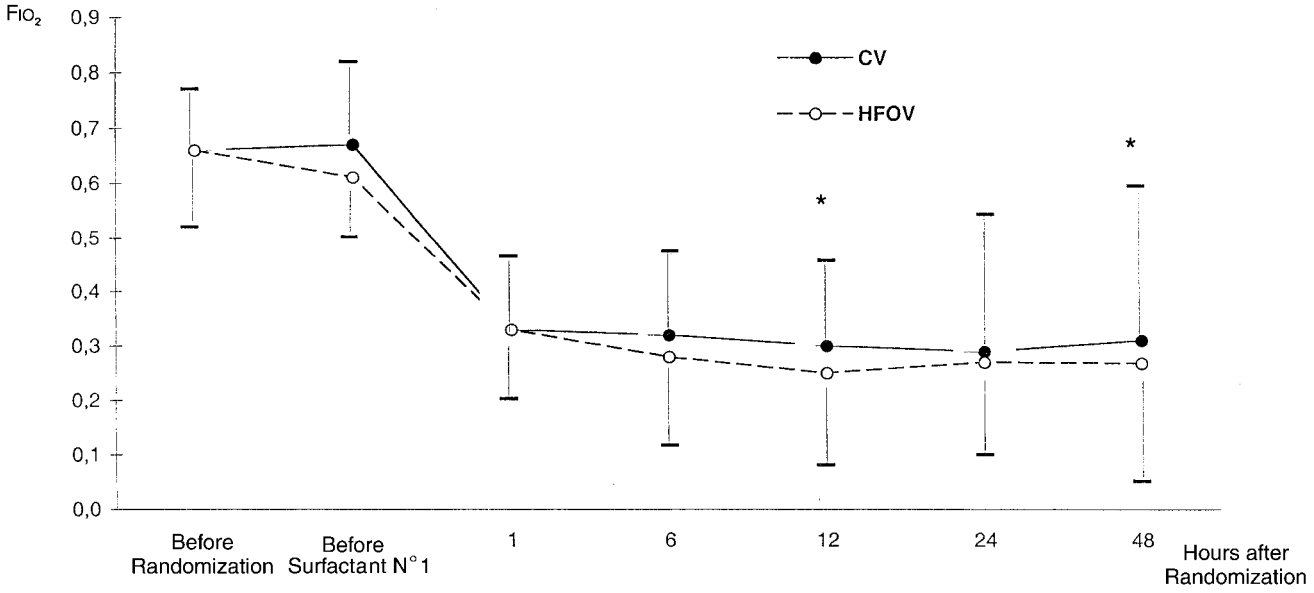

Fig 4. Mean values and SD for fractional inspired oxygen from inclusion to 48 hours of life. The asterisk indicates significant differences ($P < .05$).

TABLE 3. Respiratory Outcome: Days 0 to 9

	Conventional (n = 134) n (%)	High-Frequency (n = 139) n (%)	OR [95% CI]	Adjusted OR [95% CI]*
Treatment change	42† (31)	34‡ (24)	.71 [.42–1.21]	.78 [.43–1.44]
Respirator switch	39 (29)	21 (15)	.43 [.24–.78]	.51 [.26–.99]
Steroids	5 (4)	3 (2)	.57 [.14–2.41]	.71 [.15–3.32]
Nitric oxide	14 (10)	12 (9)	.82 [.36–1.84]	.74 [.31–1.82]
Weaning				
Extubated	81 (60)	101 (73)	1.74 [1.05–2.89]	3.53 [1.72–7.26]
Reintubated	30 (22)	49 (35)	1.89 [1.11–3.21]	2.15 [1.14–4.06]

* Adjustment on: mode of ventilation, blood pressure high or not high during pregnancy, Apgar score ≤6 or ≥7 at 5 minutes, birth weight ≤1000 and >1000 g, postmenstrual age <28 weeks and ≥28 weeks, inborn or outborn, use or no use of antenatal steroids, and Po_2:FIo_2 <100 or ≥100.
† Change in agreement with the protocol: 35 of 42 (treatment failure criteria met: see "Methods").
‡ Change in agreement with the protocol: 19 of 34 (treatment failure criteria met in 14 cases; no oscillator available after weaning failure in 5 cases).

ratio <200, rather than prophylaxis for which no exogenous surfactant is approved in our country. Surfactant administration was delayed by 20 minutes in the high-frequency group, because of the lung volume recruitment procedure (Table 1). Exogenous surfactant requirement was thereafter markedly reduced in the high-frequency group. The similar Po_2:FIo_2 ratio in the 2 groups before the second instillation supports the unbiased nature of this finding, which confirms previous results[9] and could be explained by a reduction in acute lung injury[2] or, more simply, by the use of a higher mean airway pressure in the high-frequency group.

The choice of exogenous surfactant requirements as a primary endpoint is debatable, in view of the short-term nature of this endpoint and the expected reduction of exogenous surfactant requirements in the high-frequency group, because of the use of a higher mean airway pressure. The Po_2:FIo_2 ratio, which was used as an eligibility criterion and to define the requirement for repeated surfactant instillations, does not take into account mean airway pressure, despite the importance of this variable in determining oxygenation. However, we chose not to include this variable, to address the following issue: in comparison with conventional ventilation, does high-frequency oscillatory ventilation—probably associated with the use of less surfactant, because of higher mean airway pressure—give similar or different results in terms of pulmonary outcome and complication rate, including cerebral complications? Similar results with the use of less surfactant would have been of interest in terms of cost. In addition, we believed that it was interesting to compare the 2 ventilation modes using both short-term and long-term endpoints.

Oxygen requirement at 28 days is also a short-term endpoint. Pulmonary outcome, therefore, was assessed over a longer-term by several criteria, including oxygen requirement at 36 weeks. Short-term evaluation of neurological outcome was based on assessment of severe intraventricular hemorrhage and periventricular leukomalacia. Longer-term evaluation, based on the neurodevelopmental assessment at 2 years of age of the infants included in the present study, will be reported separately.

TABLE 4. Respiratory Outcome From Days 10 to 42 Weeks' Postmenstrual Age in Survivors

	Conventional (n = 105) n (%)	High-Frequency (n = 107) n (%)	P Value
Systemic steroid use after day 9	50 (48)	56 (52)	.49
Duration of respiratory support and oxygen requirement (d)	Median (Interquartile)	Median (Interquartile)	
Mechanical ventilation			
Duration	9 (17)	9 (16)	.79
Age at weaning	10 (23)	11 (24)	.60
Oxygen			
Duration	22 (47)	22 (41)	.53
Age at weaning	31 (49)	29.5 (50)	.68
Weaning from any respiratory support (age)*	29 (25)	31 (36)	.47
Chest radiographs at 28 d	n (%)	n (%)	
n of survivors with chest radiograph†	106	108	
Absence of bronchopulmonary dysplasia‡	49 (46)	50 (46)	.99
Edwards score assessed	91	90	
Edwards score = 0	26 (29)	28 (31)	.71
	Median (interquartile)	Median (interquartile)	
Median value of Edwards score values between 1 and 9	2 (3)	2 (2)	.32

* Including nasal continuous positive airway pressure.
† n of survivors at 28 days: 110 and 111.
‡ As diagnosed in the different centers.

TABLE 5. General Outcome

Complications	Conventional (n = 134) n (%)	High-Frequency (n = 139) n (%)	OR [95% CI]	Adjusted OR [95% CI]*
Patent ductus arteriosus	55 (41)	52 (37)	.86 [.53–1.40]	.78 [.43–1.40]
Necrotizing enterocolitis	5 (4)	5 (4)	.96 [.27–3.41]	.76 [.15–3.89]
Retinopathy of prematurity	21/115 (18)	20/115 (17)	.94 [.48–1.85]	1.02 [.44–2.37]
Periventricular leukomalacia	18 (13)	14 (10)	.72 [.34–1.50]	.42 [.17–1.05]
Vasopressor use (maximum dose)†	Median (interquartile)	Median (interquartile)	P Value	
Dopamine	5 (6)	6 (5)	.78	
Dobutamine	10 (8)	10 (4)	.96	
Survival	n (%)	n (%)	OR [95% CI]	Adjusted OR [95% CI]*
	105 (78)	107 (77)	.92 [.52–1.51]	1.33 [.64–2.79]
Duration (d)	Median (interquartile)	Median (interquartile)	P Value	
In intensive care unit	37 (32)	33 (34)	.87	
In hospital	84 (42)	85 (30)	.88	

* Adjustment on: mode of ventilation, blood pressure high or not high during pregnancy, Apgar score ≤6 or ≥7 at 5 minutes, birth weight ≤1000 and >1000 g, postmenstrual age <28 weeks and ≥28 weeks, inborn or outborn, use or no use of antenatal steroids, and Po_2:FIo_2 <100 or ≥100.
† Measured in μg/kg/minute.

Survival without oxygen at 28 days and bronchopulmonary dysplasia scoring results did not differ between our 2 groups, in agreement with the message of previous reports[6,8,12] and contrary to trials reporting a benefit with high-frequency ventilation.[7,9] A similar incidence of air leak was observed in our 2 groups, in line with previous trials.[8,9,11] A higher incidence of air leak and discordant data concerning the role of ventilation mode were reported in the absence of exogenous surfactant.[6,7,9]

The observed reduction in the incidence of chronic lung disease at 36 weeks when using high-frequency ventilation was close to significance after adjustment. In addition, 1 of the 3 treatment change options, respirator switch (crossover), was significantly more frequent in the conventional group. Because crossover weakens the analysis of the study endpoints based on intent-to-treat, the magnitude of a possible pulmonary benefit of high-frequency ventilation was reduced. This might have played a role in the lack of significant difference in the incidence of chronic lung disease at 36 weeks between the 2 arms. However, the nonsignificant trend toward a reduction in the incidence of chronic lung disease at 36 weeks when using high-frequency ventilation was not supported by our finding of lack of any difference between the 2 groups for all other criteria of pulmonary outcome. Some trials previously reported benefits of high-frequency ventilation in terms of reduction in the incidence of chronic lung disease at 36 weeks,[7,9,10] whereas other trials did not confirm this finding.[11,12,15]

The discordance of the results concerning pulmonary outcome in previous clinical trials[6–12] and in the present trial could be caused by several factors, which can also influence the incidence of adverse outcome.

Infants were more immature in a recent study[12]

TABLE 6. Endpoints According to Postmenstrual Age Stratification

	<28 Weeks' Postmenstrual Age		≥28 Weeks' Postmenstrual Age		OR (95% CI)	*P* Value*
	Conventional (n = 72)	High-Frequency (n = 81)	Conventional (n = 62)	High-Frequency (n = 58)		
Primary endpoints	n(%)	n(%)	n(%)	n(%)		
Requirement of ≥2 surfactant instillations	51 (71)	27 (33)	32 (52)	15 (26)	.25 (.15–.42)	.001
In survivors	(n = 53)	(n = 60)	(n = 57)	(n = 51)		
Absence of supplemental oxygen requirement at 28 d	20 (38)	27 (45)	40 (70)	33 (65)	1.05 (.60–1.81)	.87
Secondary endpoints						
Supplemental oxygen requirement at 36 wk†	20 (38)	17 (30)	10 (18)	7 (14)	.69 (.37–1.31)	.26
Incidence of grade 3–4 intraventricular hemorrhage	15 (21)	26 (32)	4/61 (7)	8 (14)	1.91 (1.02–3.59)	.044

* Adjusted on postmenstrual age.
† Survivors at 36 weeks: n = 52, 57, 55, and 51.

and in the present trial than infants in 1 trial, which reported benefits of high-frequency ventilation using a lung volume recruitment strategy.[9]

The interval between birth and initiation of high-frequency ventilation and surfactant was >2 hours in our trial, which may blunt the benefits of high-frequency ventilation,[2,16,17] although they have been previously demonstrated with a similar delay.[9]

Antenatal corticosteroids were used in 53% of cases, a higher proportion than in 1 previous trial,[9] but lower than in another recent trial.[11] Lower proportions of antenatal steroid use are expected when considering a population of premature infants developing respiratory distress syndrome, as in our study, rather than a population of premature infants who require mechanical ventilation.[12] Antenatal corticosteroid use was taken into account when calculating our adjusted OR.

Use of exogenous surfactant also differs in the various studies. This difference and the difference in maturity of the infants may explain the reported reduction in the risk of chronic lung disease at 28 days or at 36 weeks when using high-frequency oscillatory ventilation with a lung volume recruitment strategy.[18,19]

Differences in the techniques used for high-frequency ventilation may also explain differences in the results. For example, the results obtained with a high-frequency flow interrupter[12] may differ from those obtained with true oscillators. The OHF1 oscillator used in the present trial was designed based on the experience of the Toronto group.[13,20] Adequate performances of this device, compared with those of the widely available SensorMedics 3100A oscillator (SensorMedics Critical Care, Yorba Linda, CA), were demonstrated in a bench evaluation[21]; and good clinical efficacy has been reported.[22,23]

The lack of pulmonary benefit of high-frequency ventilation compared with conventional ventilation has been attributed to the absence of lung volume recruitment strategy. Results of animal experiments[2,3] and some clinical trials[7,9] or reports[24] support the use of rather aggressive efforts to recruit lung volume. Our efforts to recruit lung volume were tailored to the severity of the respiratory disease to prevent adverse effects. The level of mean airway pressure in the high-frequency group was similar to levels used in previous studies, which either showed[9] or failed to show[12] a benefit of high-frequency ventilation.

Because early extubation may minimize lung injury, we defined objective criteria to decide on extubation in the 2 groups. Our durations of assisted ventilation using conventional or high-frequency ventilation were similar, and comparable with those in another trial that did not show a benefit of high-frequency.[12] In contrast, the Provo trial showed a benefit of high-frequency in infants weighing <1 kg, with a more than twofold longer duration on conventional ventilation than on high-frequency ventilation.[9] Less than optimal use of conventional ventilation or lack of objective criteria to decide on extubation may explain the better results observed in the high-frequency group in this trial, rather than a real superiority of high-frequency ventilation.

Grades 3 to 4 intraventricular hemorrhages occurred more frequently in the high-frequency group. In view of the similar result of the HIFI trial,[6] when designing our study, we retrospectively verified that our very premature infants did not present any difference in the incidence of grades 3 to 4 intraventricular hemorrhages according to ventilation mode, in agreement with the results of studies using a lung volume recruitment strategy.[7–9] Because this study was not designed to detect an increased risk of intraventricular hemorrhage, the sample size was not calculated for this purpose. The review board did not detect this risk because of the small difference observed.

Infants were not eligible when severe intraventricular hemorrhage was already present at the time of randomization, but the protocol accepted that randomization could be performed when head ultrasounds could not be obtained. All head ultrasounds, therefore, were reviewed to determine the time of onset of intraventricular hemorrhage. The development of grades 3 to 4 intraventricular hemorrhages after randomization was established for 14 of 19

cases in the conventional group, and 25 of 34 cases in the high-frequency group, a similar distribution to that of the total number of cases.

After adjustment for pregnancy-induced hypertension, birth weight, Apgar score, postmenstrual age, inborn status, use of antenatal corticosteroids, and Po_2:FIo_2 ratio, the risk of grades 3 to 4 intraventricular hemorrhage was not significantly increased for neonates exposed to high-frequency oscillatory ventilation (OR: 1.5; 95% CI: .68–3.30). Adjustment for pregnancy-induced hypertension, which was more frequent in the mothers of our infants receiving conventional ventilation, was decided because of its possible protective effects against intraventricular hemorrhage.[25,26]

Although the difference was not significant after adjustment, our results suggest the specific role of high-frequency ventilation on the development of severe intraventricular hemorrhage. The intent-to-treat analysis of cases switched from conventional to high-frequency ventilation (see above) indeed reduced the magnitude of the difference between the 2 groups, because the development of grades 3 to 4 intraventricular hemorrhage after switching was considered to occur in the randomization-determined arm. The role of high-frequency ventilation is also supported by the fact that more cases were observed in infants treated by high-frequency ventilation after either randomization or a switch from conventional ventilation.

Four trials using high-frequency ventilation with a similar lung volume recruitment strategy did not report any increased risk of severe intraventricular hemorrhage.[7–9,12] Appropriate comparisons, however, are not possible in 3 of these studies, because of the small sample size[7] or low incidence of severe intraventricular hemorrhage in more mature infants.[8,9]

Decreased venous return, which may account for an increased risk of intraventricular hemorrhage with high-frequency ventilation, can be prevented in animals by appropriate changes in mean airway pressure,[27] but this has not been clearly confirmed in infants.[28] As recommended,[7] we frequently assessed lung inflation and decreased mean airway pressure as the infant's state improved. Our low incidence of air leak and the lack of difference in vasopressor drug use[6] suggest that overinflation of the lungs was unusual in our infants receiving high-frequency ventilation. However, elective use of a lung volume recruitment strategy followed by exogenous surfactant may have resulted in a short period of reduced venous return to the heart and increased intracerebral blood pressure, which could have facilitated the development of severe intraventricular hemorrhage.

Variations in Pco_2 may alter cerebral blood flow and increase the risks of intraventricular hemorrhage and periventricular leukomalacia.[15,29] In our trial, Pco_2 did not differ between the 2 groups before randomization. Variations during the following 12 hours were less marked in the conventional group than in the high-frequency group, with significantly lower values in the latter group. The maximum difference was 4 mm Hg (median: 39 vs 34 mm Hg), 6 hours after randomization. This highlights the powerful effect of high-frequency oscillatory ventilation on carbon dioxide elimination, and the resulting difficulty to strictly control Pco_2. But the Pco_2 values were both below the range suggested in the protocol, reflecting also the rapid improvement, which usually follows surfactant administration. The Pco_2 observed in the high-frequency group were not as low as values associated with an increased risk of intraventricular hemorrhage.[30] Moreover, adjustment for maximum variations of Pco_2 did not modify our result concerning the incidence of severe intraventricular hemorrhage. Finally, the incidence of periventricular leukomalacia was similar in our 2 groups of infants, which does not support a major adverse effect of carbon dioxide variations in our infants receiving high-frequency ventilation.

CONCLUSION

The use of high-frequency oscillatory ventilation reduced exogenous surfactant requirements but did not modify pulmonary outcome. In addition, the risk of severe intraventricular hemorrhage seemed to be increased. We, therefore, suggest that conventional ventilation should constitute the first choice in premature infants with respiratory distress syndrome, whereas high-frequency ventilation could be used in cases failing to obtain a good response to this mode of ventilatory support.

ACKNOWLEDGMENTS

This work was supported by grants from Serono France Laboratories, Plan Hospitalier de Recherche Clinique, and Assistance-Publique-Hôpitaux de Paris.

We gratefully acknowledge the contribution of Stéphane Lebouedec, MD (Saint-Vincent-de-Paul Hospital, Paris); Olivier Claris, MD (Edouard Herriot Hospital, Lyon); and the teams of the participating centers.

We thank Anthony Saul, MBBS, for stylistic review of the manuscript.

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Soranus advised that the newborn infant be salted and bathed in warm water. He deplored the plunging of the infant into wine or cold water as "a barbarous custom of Teutonic tribes designed to test vigor."

Soranus of Ephesus (2nd century), quoted by Desmond MM. *Newborn Medicine and Society.* Austin, TX: Eakin Press; 1998

Submitted by Student

Prospective Randomized Multicenter Comparison of High-Frequency Oscillatory Ventilation and Conventional Ventilation in Preterm Infants of Less Than 30 Weeks With Respiratory Distress Syndrome

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Pediatrics 2001;107;363-372
DOI: 10.1542/peds.107.2.363