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A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure

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Summary

A multicenter randomised trial was conducted in nine neonatal centers in Japan to re-evaluate the safety and the efficacy of high frequency oscillatory ventilation using the piston type oscillator (Hummingbird) in the treatment of respiratory failure in preterm infants weighing between 750 and 2000 g at birth. A total of 92 infants were enrolled in the study. Forty-six infants were allocated to high frequency oscillatory ventilation and 46 infants to conventional mechanical ventilation. There were no differences in sex, birth weight, gestation and Apgar score between groups. The study was begun 2.0 ± 1.6 h (mean ± S.D.) after birth in the high frequency oscillation group and 1.7 ± 1.5 h after birth in the conventional mechanical ventilation group. The absence of intraventricular hemorrhage was confirmed by echography in all cases before beginning ventilation. Mortality was similar in high frequency oscillatory ventilation and conventional mechanical ventilation (0 and 2%). The incidence of intraventricular hemorrhage was also similar in the high frequency and conventional mechanical ventilation groups (15 and 13% overall; 4 and 2% in grades III and IV, respectively). Nine percent of the infants in high frequency oscillatory ventilation and 13% in conventional mechanical ventilation developed bronchopulmonary dysplasia, but the difference was not significant. The frequency

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of air leaks was also equal in both groups. Periventricular leukomalacia was detected in 9% of infants on conventional mechanical ventilation and 2% on high frequency oscillation, but the difference was not significant. Mean airway pressure was significantly higher in the high frequency oscillatory ventilation group and the infants on high frequency oscillation showed a significantly higher arterial to alveolar oxygen tension ratio after 6 h of treatment. These results suggest that high frequency oscillatory ventilation does not increase the risk of severe complications such as air leaks, intraventricular hemorrhage or periventricular leukomalacia when it is used by experienced neonatologists. Indeed high frequency oscillatory ventilation helps provide better oxygenation with higher mean airway pressure without increasing the risk of bronchopulmonary dysplasia and severe complications such as air leaks and intraventricular hemorrhage.

Key words: high frequency oscillatory ventilation; conventional mechanical ventilation; preterm newborn infant; pulmonary air leak; bronchopulmonary dysplasia; intraventricular hemorrhage; periventricular leukomalacia

Introduction

Improvements in respiratory care, especially mechanical respiratory care, in the recent years has brought about a remarkable reduction in the mortality of sick preterm newborn infants. Unfortunately, however, the improvement in survival from mechanical ventilation has created a new problem; the increasing incidence of bronchopulmonary dysplasia or chronic lung disease, partly affected by barotrauma due to high pressure large volume ventilation. In order to reduce the incidence of bronchopulmonary dysplasia, the mode of ventilation presently applied for very low birth weight infants should be improved.

A new mode of ventilation which is called high frequency oscillation or high frequency oscillatory ventilation is considered to be less barotraumatic because pressure swings at the alveolar level are minimal [4,9]. Studies in animals and human newborn infants revealed that high frequency oscillatory ventilation is effective in oxygenation and gas exchange without causing barotrauma even in situations when conventional mechanical ventilation has failed [2,3,8,14,16].

However, the collaborative multicenter randomised trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation by the HIFI Study Group failed to show the effectiveness of high frequency oscillatory ventilation [15]. On the contrary, the study suggested there was an increased incidence of air leaks, intraventricular hemorrhage and periventricular leukomalacia [15].

The unexpected results from the HIFI Study Group prompted us to conduct a similar multicenter randomised trial in Japan to re-evaluate the safety and the efficacy of high frequency oscillatory ventilation in preterm infants with respiratory failure. Thus far, there had been no reports in Japan which described an increased incidence of air leaks or intraventricular hemorrhage with the use of the piston type oscillator which was first introduced to neonatal respiratory care in 1985.

Subjects and Methods

Nine neonatal centers in Japan which have sufficient experience with both high frequency oscillatory ventilation and conventional mechanical ventilation in the treatment of respiratory failure of preterm infants participated in the study.

Preterm infants with birth weights between 750 and 2000 g with respiratory distress requiring ventilator care soon after birth who were born from April, 1989 to March, 1990 and cared for at these nine neonatal centers were selected as candidates. Those who were screened and found to show no evidence of intraventricular hemorrhage by brain echography within 60 min of birth for the inborn infants and within 6 h for outborn infants were eligible for randomisation with opaque sealed envelopes stratified for birthweight (750–1249 g and 1250–1999 g). Mechanical ventilation in the form of either high frequency oscillation or conventional mechanical ventilation was begun within 60 min in inborn and within 6 h after birth in outborn infants. Infants were excluded from the study according to the protocol described in the HIFI Study [15].

Assuming a power of 80% and a significance level of 5%, and based on the previously reported incidences of grades III and IV intraventricular hemorrhage on CMV with exogenous surfactant replacement therapy as 11% [7] and on HFOV as 26% [15], we estimated that a total sample of approximately 80 patients would be needed for the reconfirmation of HIFI result.

HFOV was carried out with a piston type oscillator, Hummingbird BMO 20 N (Senko Medical Instrument Manufacturing Company, Ltd., Tokyo, Japan). Conventional mechanical ventilation was delivered by time-cycled pressure-limited ventilators, Bear Cub (Bear Medical Systems, Inc., Riverside, California, USA) or Sechrist Infant Ventilator (Sechrist Industries, Inc., Anaheim, California, USA). Ventilator settings were controlled to obtain arterial oxygen tension (P_aO_2) between 8.0 and 13.3 kPa and arterial carbon dioxide tension (P_aCO_2) between 4.6 and 6.7 kPa. Lung volume was recruited in high frequency oscillatory ventilation by inflating the lungs fully by manual bagging just before starting and a high mean airway pressure was adopted [6,10]. Frequency was fixed to 15 Hz. Infants were crossed over to the alternate ventilator when they failed to respond. Criteria for failure were the same as in the HIFI study [15]. Muscle relaxants were not used.

In the present trial, we were allowed a change from high frequency oscillatory ventilation to conventional mechanical ventilation for weaning when F_iO_2 could be reduced less than 0.3, mean airway pressure less than 0.7 kPa and stroke volume less than 2 ml/kg or amplitude less than 3 kPa.

All infants were cared for in servo-controlled incubators with a relative humidity greater than 80%. Skin temperature was maintained between 36.0 and 36.5°C. Intravenous drip infusion was maintained until the volume of oral feeding exceeded 100 ml/kg per day. Infusion was started with 5 to 10% glucose in water 50 ml/kg per day on day 1 and increased by 5–10 ml/kg per day. The maximum volume infused was approximately 120 ml/kg per day during the first 10 days. The infant's mother's breast milk was given whenever possible for oral feeding.

Pulmonary surfactant replacement therapy with reconstituted bovine surfactant (Surfacten; Tokyo Tanabe Pharmaceutical Company Ltd., Tokyo, Japan) was indicated when the diagnosis of respiratory distress syndrome was clinically made.

Brain echography was repeated every day for the first week of life and as needed thereafter. Intraventricular hemorrhage was classified into grades I to IV as proposed by Papile et al. [13].

Symptomatic patent ductus arteriosus was treated with oral administration of mefenamic acid or with rectal suppositories of indomethacin. None of the infants in the study required surgical ligation.

Chest X-ray was evaluated at least once between 28 and 30 days of life for the detection of bronchopulmonary dysplasia. Bronchopulmonary dysplasia was defined as the condition in which the infant developed chronic respiratory distress requiring extra oxygen inhalation after 28 days of age, with chest X-ray findings of emphysema and fibrosis compatible with stages III or IV in the classification by Northway and co-workers [12].

All infants enrolled in the study, except for one who died before discharge, were seen at follow-up clinic of each medical center at the ages of 3, 6 and 12 months for the evaluation of growth and development and for the detection of sequelae. The Mantel-Haenszel test was used to compare discrete baseline and outcome variables between the two groups. This study was approved by each hospital enrolled according to their clinical study guidelines and informed consent was obtained from at least one parent.

Results

A total of 118 infants were selected as candidates, but 16 of them met the exclusion criteria, thus 92 infants were enrolled. Half of them, 28 boys and 18 girls were

TABLE 1

Characteristics of the study groups (all comparisons were statistically nonsignificant).

Characteristics	HFOV	CMV
Number of infants (%)		
Total	46	46
Male	28 (61)	27 (59)
Female	18 (39)	19 (41)
Inborn	31 (67)	31 (67)
Outborn	15 (33)	15 (33)
RDS	32 (70)	34 (74)
Surfactant Treated	36 (78)	36 (78)
Mean ± S.D.		
Birth weight (grams)	1243 ± 322	1258 ± 318
Gestation (weeks)	29.0 ± 2.3	29.0 ± 2.1
Apgar score		
1 minute	5.1 ± 2.6	5.1 ± 2.2
5 minutes	6.9 ± 2.1	7.5 ± 1.8
Age at entry (hours)	2.0 ± 1.6	1.7 ± 1/5

HFOV, High frequency oscillatory ventilation; CMV, conventional mechanical ventilation; RDS, respiratory distress syndrome.

TABLE 2

Major outcomes and major complications (number of infants (%)).

Characteristics	HFOV	CMV	*P*-value
All infants	46	46	
Cross-over	4 (9)	1 (2)	0.17
Death <28 days	0 (0)	1 (2)	0.32
Air leaks	4 (9)	6 (13)	0.51
Symptomatic PDA	16 (35)	11 (24)	0.26
Pulmonary hemorrhage	0 (0)	2 (4)	0.15
Pneumonia	4 (9)	6 (13)	0.49
IVH (any grade)	7 (15)	6 (13)	0.77
Grade I	3 (7)	3 (7)	0.98
Grade II	2 (4)	2 (4)	0.94
Grade III	2 (4)	1 (2)	0.56
Grade IV	0 (0)	0 (0)	—
PVL	1 (2)	4 (9)	0.17
Extra O_2 on day 28	17 (37)	15 (32)	0.66
MV on day 28	13 (28)	9 (20)	0.33
BPD	4 (9)	6 (13)	0.51

PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia.

allocated to high frequency oscillatory ventilation. The other 46 infants, 27 boys and 19 girls were assigned to conventional mechanical ventilation. The number of study subjects differed considerably among nine centers; from four to 32 patients per center. The characteristics of the subjects were all statistically similar in the two treatment groups (Table 1). There were four cases of cross over from high frequency oscillatory ventilation to conventional mechanical ventilation and one case of cross over going the other way.

Table 2 summarizes the major results. There was one death in the group with conventional mechanical ventilation. There were no significant differences in the incidence of air leaks (9% versus 13%), pulmonary hemorrhage (0 versus 4%), pneumonia (9% versus 13%) or symptomatic patent ductus arteriosus (35% versus 24%) between high frequency oscillatory and conventional mechanical ventilation groups. None of the infants in either group developed pneumoperitoneum.

Duration of ventilator support was similar in both groups; 17.3 ± 24.4 days (mean ± S.D.) for HFOV group and 13.5 ± 21.0 days for CMV group, respectively. None of the infants failed extubation.

There were 17 infants on extra oxygen supply and 13 infants on mechanical ventilation at 28 days of age in the group of high frequency oscillation. Most of them had apnea of prematurity requiring F_iO_2 less than 0.3 and only four (9%) of them had bronchopulmonary dysplasia. In the conventional mechanical ventilation group, extra oxygen supply was given to 15 infants and nine infants were still on a ventilator at 28 days of age. Six (13%) were diagnosed as having bronchopulmonary

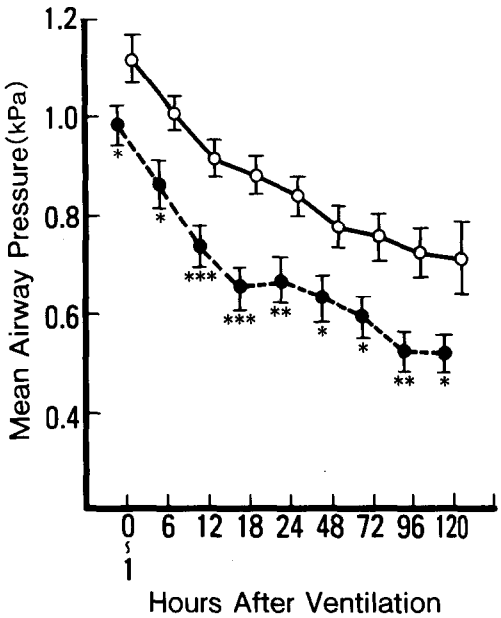

Fig. 1. Mean values for the mean airway pressure at the onset of treatment and for 120 h after treatment by high frequency oscillatory ventilation (O) and conventional mechanical ventilation (●). Symbols are the same as in Fig. 1. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

dysplasia. Although the incidence of bronchopulmonary dysplasia was slightly higher in the conventional mechanical ventilation group, the difference was not significant.

The incidence of intraventricular hemorrhage was also similar in both groups; 15% in the high frequency oscillatory ventilation and 13% in the conventional mechanical ventilation group. There were two infants who had intraventricular hemorrhages of grade III in the high frequency oscillatory ventilation and one in the conventional mechanical ventilation group, but none of the infants in either group developed grade IV intraventricular hemorrhage. Infants in the conventional mechanical ventilation group showed a slightly higher incidence of periventricular leukomalacia in comparison to the high frequency oscillatory ventilation group (9% versus 2%), but the difference was not significant.

Inspired oxygen concentrations prior to the treatment were more than 90% in both groups, but sharply declined to below 50% by 6 h of treatment. No difference was found in the two treatment groups (Fig. 1).

However, the mean airway pressure applied in both groups was significantly different from the onset of treatment. As shown in Fig. 1, the comparison of mean airway pressure in the two groups revealed a significantly higher level in the high frequency oscillatory ventilation group through to 120 h after the onset of treatment. Arterial to alveolar oxygen tension ratios ($P_{a/A}O_2$) in the two groups also showed

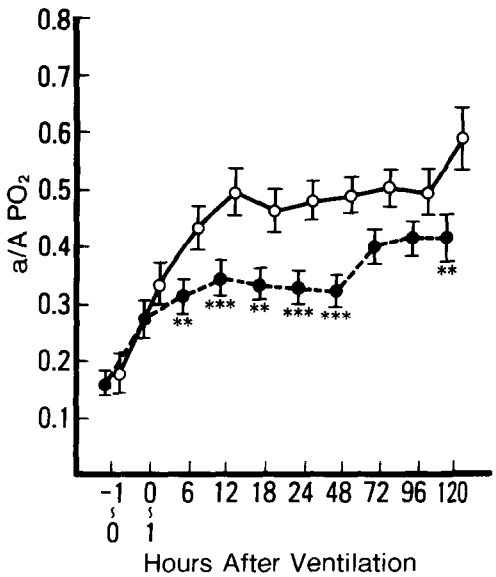

Fig. 2. Mean values for the arterial to alveolar oxygen tension ratio (a/APo_2) before treatment and for 120 h after treatment. Symbols are same as in Figs 1 and 2.

significant differences. Better values were obtained in the high frequency oscillatory ventilation group starting at 6 h through to 120 h after the onset of ventilation (Fig. 2).

There were no significant differences in P_aCO_2 values between the two groups and the values were kept in the desired range of 4.6 to 6.7 kPa after the onset of treatment.

Follow-up evaluations of the enrolled infants at the age of 12 months revealed that four infants in each group (8.7% in high frequency oscillatory ventilation and 8.9% in conventional mechanical ventilation) had delays in motor and/or mental development (Table 3). Abnormal fibrous or emphysematous shadows on chest X-ray were still present in two infants on high frequency oscillation and four infants on conventional mechanical ventilation, but none of the survivors in either group required extra oxygen inhalation at the age of 12 months.

TABLE 3

Results of 1-year follow-up (all comparisons were statistically nonsignificant) (number of infants (%)).

Characteristics	HFOV	CMV
Total discharged	46 (100)	45 (98)
Evaluated at 1-year-old	46 (100)	45 (100)
Developmental delay	4 (9)	4 (9)
Abnormal chest X-ray	2 (4)	4 (9)
Extra O_2 needed	0 (0)	0 (0)

Discussion

Animal experiments have suggested that high frequency oscillatory ventilation provides better oxygenation with fewer complications than conventional mechanical ventilation [2,8,11,16]. However, the first controlled trial in human preterm infants in North America failed to confirm the advantages. On the contrary, the study suggested the possibility of an association of high frequency oscillatory ventilation with complications such as air leaks, intraventricular hemorrhage and periventricular leukomalacia [14].

The present study was designed to reevaluate the results obtained by the HIFI Study. The primary purpose of the present study, however, was not to examine the effects of high frequency oscillatory ventilation on the incidence of bronchopulmonary dysplasia, but to observe the incidence of complications reported to be higher in high frequency oscillatory ventilation. Therefore, the number of infants enrolled in the present study could be much smaller than in the HIFI Study.

In the present trial, no significant differences were demonstrated in the incidence of air leaks, intraventricular hemorrhage or periventricular leukomalacia between the two groups. These results show that high frequency oscillatory ventilation is just as safe as conventional mechanical ventilation in regard to these complications. A recent report by Clark and his associates also concluded that use of HFOV as the predominant mode of ventilation in the management of respiratory distress syndrome of the preterm infant is as safe as CMV [1]. The rates of air leaks and intraventricular hemorrhage in infants on conventional mechanical ventilation in this study were similar to those found in the surfactant treated group of a multicenter randomized controlled trial of surfactant replacement therapy conducted in Japan from 1985 to 1986 [7]. These rates are much lower than the ones in the HIFI Study and in that of Clark of his associates. The difference in the incidence of complications between the North American and the Japanese studies may be due to differences in routine management and intensive care of sick preterm infants and to the uniformity of the level of participating neonatal centers. It was reported that the rates of grade III and IV intraventricular hemorrhage ranged from 6 to 48% between centers in the HIFI Study. These differences are far larger than that between study groups [5] suggesting that population or management differences between centers may be important for the evaluation of complications of new and radically different technologies such as high frequency oscillatory ventilation.

Clark et al. reported the significant reduction in the incidence of CLD in their recent control study [1]. Though the sample size was similar, no significant difference was demonstrated in the present study. They used a different type of piston oscillator and adopted a different frequency and inspiration-expiration ratio, and these differences might influence the results. Another explanation might be the fact that switching to CMV was allowed for weaning in our trial, thus our HFOV group was compatible to HFOV/CMV group in Clark's trial.

However, the most striking difference was the use of exogenous surfactant replacement therapy in infants with respiratory distress syndrome in our trial. None received surfactant therapy in Clark's series. Lower incidence of BPD even in the CMV group of our study in comparison to the HIFI Study and Clark's trial sug-

gested the influence of surfactant replacement therapy. Surfactant for replacement therapy has been available at all Level II and III neonatal centers in Japan as a drug of first choice for the treatment of respiratory distress syndrome of newborn infants since 1987. Therefore, a clinical trial with a protocol which prohibits the use of surfactant is not ethical. Although the number of subjects was too small to make a statistical comparison, no differences were seen in the incidence of intraventricular hemorrhage between the surfactant treated and non-treated infants in each group.

In this trial, mean airway pressure was significantly higher in the high frequency oscillation group from the beginning to 120 h after the treatment. This was the reflection of our policy that mean airway pressure should be kept higher during high frequency oscillatory ventilation to attain lung volume recruitment. Caution was taken to avoid intracranial venous congestion by keeping the infant in a head-up position. This type of careful management may have contributed to lessening the incidence of complications.

It should be noted that even with higher mean airway pressure the incidence of air leaks was not higher than in conventional mechanical ventilation. On the contrary, arterial to alveolar oxygen tension ratios were significantly higher in infants on high frequency oscillation starting at 1 h through to 120 h after the onset of treatment, demonstrating better oxygenation in high frequency oscillation. These higher ratios were attributed to higher mean airway pressure. However, the incidence of bronchopulmonary dysplasia did not increase even with higher mean airway pressures in infants on high frequency oscillatory ventilation. These findings indicate that high frequency oscillatory ventilation can provide better oxygenation by raising mean airway pressure without increasing the risk of air leaks or chronic lung disease.

We can thus conclude that, contrary to the results of the HIFI Study, high frequency oscillatory ventilation with a piston-pump oscillator significantly improves oxygenation in preterm newborn infants with respiratory failure, but does not increase the risk of severe complications such as air leaks, bronchopulmonary dysplasia or intracranial hemorrhage when used carefully by experienced staff in neonatal centers.

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