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Comparison of Respiratory Indices in Predicting Response to High Frequency Oscillatory Ventilation in Very Low Birth Weight Infants with Respiratory Distress Syndrome

To evaluate the predictive values of oxygenation index (OI), arterial-alveolar oxygen tension ratio $(a/APO)_2$, and alveolar-arterial oxygen gradient ($(A\text{-}a)DO_2$) for early recognition of responsiveness to high frequency oscillatory ventilation (HFOV) in very low birth weight infants with respiratory distress syndrome (RDS), 23 infants who received HFOV treatment for severe RDS after failing to be improved with conventional mechanical ventilation from July 1995 to February 1998 were included. Twelve infants survived with HFOV (Responder group), while 11 infants could not maintain oxygenation with HFOV and died (Non-responder group). Clinical record (of each patient) were retrospectively reviewed and compared with the respiratory indices. Mean $(A\text{-}a)DO_2$ was significantly lower in the responder group than in the non-responder group at 2 hr after HFOV (p=0.024), and the difference was more remarkable at 6 hr (p=0.005). Death in the patient with $(A\text{-}a)DO_2$ over 350 at 2 hr after HFOV therapy was 100% in sensitivity and 80% in specificity. The earliest significant difference of mean a/APO_2 between two groups was noted at 6 hr after HFOV treatment (p=0.019). OI showed no significant differences between two groups. In summary, $(A\text{-}a)DO_2$ was the most effective and sensitive respiratory index for predicting the responsiveness to HFOV in infants with severe RDS providing clue as early as 2 hr.

Key Words: *High-Frequency Ventilation; Infant, Very Low Birth Weight; Respiratory Distress Syndrome*

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INTRODUCTION

As the neonatal intensive therapeutic modalities including mechanical ventilation improve, the mortality of premature newborn infants, especially of very low birth weight (VLBW) infants, has been dramatically decreased (1). However, pulmonary disease remained to be the major cause of death and mortality in VLBW infants (2). Increased survival of VLBW infants has been accompanied by increased population with acute or chronic complications of mechanical ventilation such as air-leak syndrome or bronchopulmonary dysplasia (3, 4). These sequelae of conventional mechanical ventilation (CMV) have resulted from ventilating an immature lung with high-peak inspiratory pressure (barotrauma) and large tidal volume (volutrauma). VLBW infants with respiratory failure such as severe RDS, requiring large tidal volume in conventional ventilation, may be at the higher risk for the development of complications (5, 6).

Various respiratory therapeutic modalities, including high frequency oscillatory ventilation (HFOV) (7-9), inhaled nitric oxide (iNO) (10), and liquid ventilation (11) have been developed for more effective and less injurious management of acute respiratory failure. HFOV is a new mechanical ventilation method using low tidal volumes less than anatomical dead space and supraphysiologic ventilatory frequencies. The goal of introducing HFOV in treating severe RDS of the newborn is to improve gas exchange with lower pressure, thereby to decrease the rate of acute and chronic ventilation-associated morbidity and mortality. Several clinical studies have been conducted on the application of HFOV for premature infants with RDS (5, 6, 12, 13). HFOV provides effective ventilation, improves oxygenation and significantly reduces the development of air leak syndrome in infants with severe RDS (6). Also it reduces the risk of residual chronic lung disease (6).

If the patient fails to improve with HFOV, other

therapeutic modalities such as iNO or liquid ventilation which augments the responsiveness to HFOV would be necessary. Combined therapies with iNO or liquid ventilation using HFOV augment the response rate (14, 15). Therefore, to know whether the patient will respond to HFOV or not as early as possible is very important. Identifying the predicting factor for response to HFOV is useful to predict the prognosis.

The purpose of this study was to evaluate the efficacy of respiratory indices for predicting the responsiveness to HFOV in VLBW infants with severe RDS.

MATERIALS AND METHODS

Study population

Twenty-three VLBW infants with severe RDS, who received HFOV within 48 hr of life after failing to respond to CMV were included in this study. They were admitted to the neonatal intensive care unit (NICU) of Samsung Medical Center from July 1995 to February 1998. All patients received surfactant replacement therapy. Diagnosis of RDS was made by typical radiographic and clinical findings (16). We retrospectively reviewed the clinical record of each patient to analyze clinical characteristics, ventilator parameters, arterial blood gas values, and respiratory indices such as alveolar arterial oxygen difference ((A-a)DO_2), arterial alveolar oxygen tension ratio (a/APO_2), and oxygenation index (OI).

Treatment strategies

All patients received surfactant replacement therapy soon after RDS was diagnosed. CMV (Infant Star, Infrasonics, U.S.A.) was initially applied. HFOV was provided when severe respiratory failure with OI over 10 on CMV settings occurred. HFOV was delivered by Sensor Medics (model 3100, Critical Care Co., U.S.A.) or Humming V (Metran Medical Instrument MFG., Japan).

In HFOV strategy, MAP HFOV initially was set at 2-3 cmH_2O above the MAP used on CMV just prior to the beginning of HFOV treatment. MAP was adjusted by 1 cmH_2O increments until optimal oxygenation and adequate lung recruitment were obtained. Adequate lung recruitment was confirmed by chest radiography which showed normal lung inflation. Level of diaphragm situated at the eighth to ninth posterior rib level. Chest X-rays were taken within 2 hr of HFOV and at least once a day. The delta P (amplitude or stroke volume) initially was selected on the basis of adequate chest wall vibration, and was adjusted later according to $PaCO_2$ values (arterial CO_2 tension). Ventilatory frequency was fixed at 15 Hz. Inspiratory to expiratory time ratio was maintained at 0.33 in SensorMedics. For the weaning from HFOV, first decreased FiO_2 below 0.7, followed by decrease mean airway pressure (MAP, 1 cmH_2O in each step) and then decreased FiO_2 and MAP alternatively. When adequate oxygenation was maintained with FiO_2 under 0.5 and MAP below 8 cmH_2O, the HFOV was switched to CMV mode.

Outcome

Patients were divided into the two groups according to their responses to HFOV. The responder group (n=12) remained on HFOV with adequate oxygenation and survived. The non-responder group (n=11) failed to respond to HFOV and died subsequently.

Respiratory indices were determined at base, 30 min, 1, 2, 6, and 12 hr after HFOV. (A-a)DO_2 was calculated as the difference between alveolar oxygen tension (PAO_2) and arterial oxygen tension (PaO_2). Alveolar oxygen tension (mmHg) was calculated by the formula: $(713 \times FiO_2)-(PaCO_2/0.8)$. The OI was calculated as $(MAP \times FiO_2 \times 100)/PaO_2$. Sensitivity, specificity, positive and negative predictive values of responsiveness to HFOV at an arbitrary set point values of respiratory indices were also calculated.

The differences of clinical characteristics and respiratory indices between the two groups were analysed using repeated-measures analysis of variance and student t-test by SPSS version 7.5. p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Of 23 VLBW infants with RDS, 12 patients (52%) responded to HFOV and 11 patients (48%) did not respond and subsequently died.

Mean gestational age and birth weight were lower in the non-responder group without statistical significance (Table 1). Pre-HFOV OI, age of starting HFOV and prevalence of clinically significant PDA did not differ between two groups.

Respiratory indices in predicting response to HFOV

Fig. 1 showed time course of changes in respiratory indices after HFOV in two groups. Significant improvement of oxygenation was observed after HFOV in the responder group during HFOV treatment. Among respiratory indices, (A-a)DO_2 was the most sensitive and

Table 1. Demographic findings and characteristics of VLBW infants with respiratory distress syndrome who received HFOV

	Responder group N=12	Nonresponder group N=11	*p* value
Gestational age (week)	28.6±0.3	27.6±0.7	NS
Birth weight (g)	1063.5±72.6	894.8±62.1	NS
HFOV			
Pre-OI	11.8±2.4	12.3±2.3	NS
Start time (hr)	32.2±7.3	26.1±11.0	NS
Duration (day)	4.0±1.4	7.6±3.3	NS
PDA (n)	12	11	NS

Values are presented as mean±SE.
Responder group were those who remainded on HFOV with adequate oxygenation and survived, and nonresponder group were those who failed to respond to HFOV and died subsequently.
VLBW infant, very low birth weight infant; HFOV, high frequency oscillatory ventilation; PDA, patent ductus arteriosus; NS, not significant

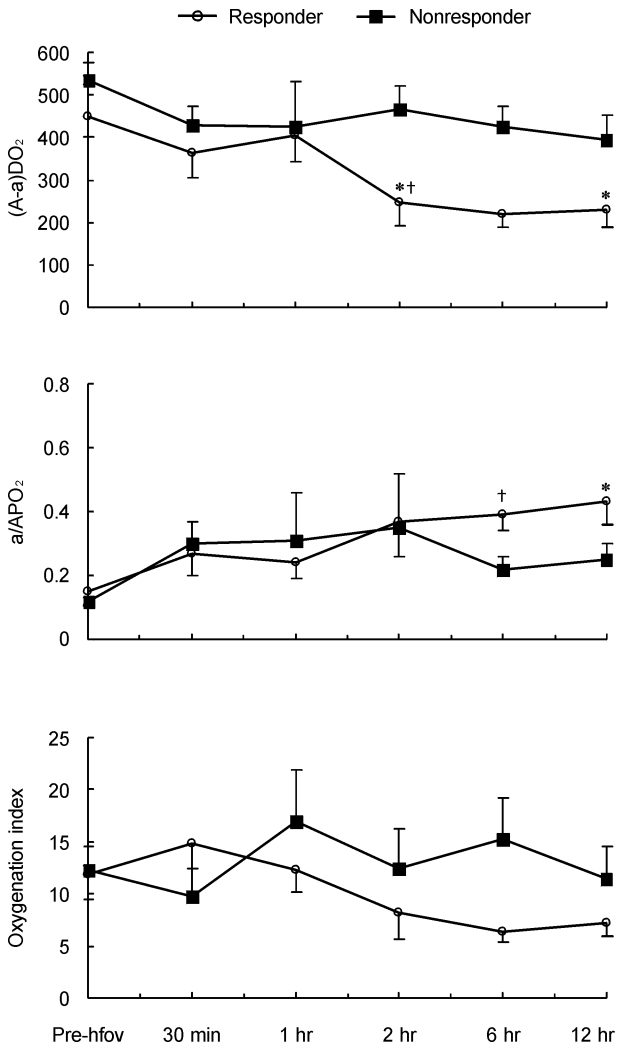

Fig. 1. Changes in alveolar-arterial oxygen gradient ((A-a)DO_2), arterial to alveolar oxygen ratio (a/APO_2), and oxygenation index in the responder and nonresponder groups over the first 12 hr on high frequency oscillatory ventilation. Data are expressed as mean±SE. *$p<0.05$ compared to corresponding baseline value; †$p<0.05$ compared between two groups.

earliest in predicting response to HFOV. At 2 hr of HFOV therapy, significant improvement of (A-a)DO_2 was observed compared to the pre-HFOV value in the responder group. (A-a)DO_2 at 2 hr after HFOV was also significantly lower in the responder group than in the non-responder group. Using cut-off value of (A-a)DO_2 over 350 at 2 hr of HFOV therapy predicted death with 100% sensitivity and 80% specificity (Fig. 2). It means that (A-a)DO_2 had a positive predictive value of 100% and negative predictive value of 80% for death.

At 6 hr after HFOV, a/APO_2 in the responder group improved significantly compared to the nonresponder group. At 12 hr after HFOV, a/APO_2 in the responder group improved significantly compared to pre-HFOV values.

OI showed a tendency to improve in the responder group but it did not reach a statistical significance.

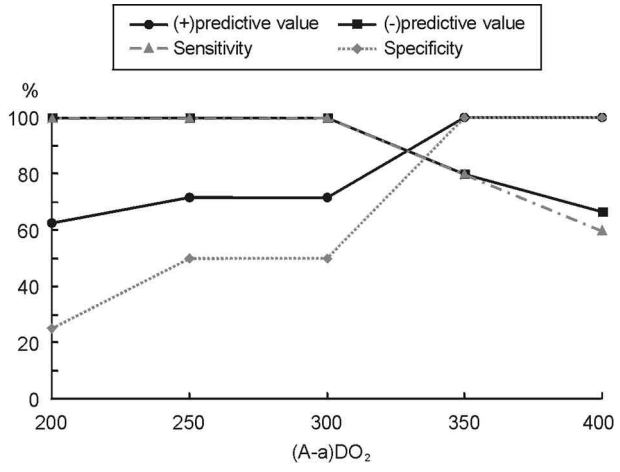

Fig. 2. Predicting response of high frequency oscillatory ventilation based on (A-a)DO_2 at 2 hr after high frequency oscillatory ventilation (HFOV). (A-a)DO_2 of >350 at 2 hr of HFOV therapy predicted death with 100% sensitivity and 80% specificity. It also had a positive predictive value of 100% and negative predictive value of 80% for death.

DISCUSSION

Our study suggested that HFOV was a very effective and safe rescue treatment modality for severe RDS of VLBW infants who did not respond to CMV.

Although the birth weight and gestational age in the nonresponder group were slightly lower than in the responder group, it did not reach a statistical significance. 52% of survival in our study was similar to the survival rate in studies of Clark et al. (6) and Chan et al. (12), 53% and 47% respectively. Otherwise, HiFO Study Group (5) and study (17) for pediatric population with severe respiratory failure reported higher survival rates than our observation. The overall survival rate was 74% in children. These results are most likely from the difference of lung maturation.

Pre-HFOV OI and time of starting HFOV did not differ between the two groups in our study. We started HFOV at average of 29 hr after birth. Clark et al. (6) demonstrated beneficial effects of HFOV on reducing the severity and prevalence of pulmonary complication of RDS with starting HFOV at an average age of 8 hr reduced the severity and frequency. We started HFOV treatment later than their study. A reduction in pulmonary injury has been demonstrated in surfactant deficient lungs when premature animals were ventilated immediately after delivery with HFOV. Jackson et al. (18) have reported beneficial additive effects when HFOV was used early in RDS after exogenous surfactant. These studies suggested that early and aggressive application of HFOV with exogenous surfactant therapy could reduce acute lung injury and therefore should improve pulmonary outcome (19). Although patients in our study received HFOV later than previous studies, starting time was not different between the responder group and the non-responder group. Therefore timing of applying HFOV was not a critical factor for the prognosis in our study.

Patent ductus arteriosus is one of the aggravating factors, which deteriorates respiratory status in preterm infants. All of our patients had hemodynamically significant PDA with no difference in the prevalence of PDA between the two groups. The responsiveness to HFOV was not influenced by the presence of PDA.

Other modalities of respiratory support have been proposed for rescuing severe respiratory failure in newborn infants. These methods include extracorporeal membrane oxygenation (ECMO), liquid ventilation and inhaled nitric oxide. There are few clinical studies reported the effects of combined use of exogenous surfactant and HFOV (20). Clark et al. emphasized that this combination increased lung volume, lung compliance and functional residual capacity (6). They also demonstrated that HFOV for the management of RDS was as safe as conventional ventilation and might decrease the occurrence of chronic lung diseases in premature neonates who required assistant mechanical ventilation.

Inhaled nitric oxide (iNO) is effective in treating the pulmonary hypertension in neonates with persistent pulmonary hypertension (21). Furthermore, iNO has been shown to improve oxygenation by decreasing intrapulmonary shunting (22). iNO improves ventilation-perfusion mismatch by preferentially diffusing across alveolar membranes of ventilated areas of lung (23). HFOV improves ventilation-perfusion matching by maintaining the lung at a constant volume (24). In both experimental and clinical studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in newborns who had pulmonary hypertension complicated by diffuse parenchymal lung diseases and underinflation such as RDS (14, 25). These combined therapies are expected to augment the response rate and improve the outcome. Introducing second respiratory therapeutic modalities effectively and determining early whether patients respond to HFOV or need adjuvant other therapy are very important.

Some reports have shown that infants with severe respiratory failure, who did not respond to conventional therapies and met the traditional qualifying criteria for ECMO, may respond to HFOV without requiring ECMO (26-28). But some of the newborns who treated with HFOV are likely to fail and will need ECMO to maintain adequate oxygenation. Stewart et al. (29) suggested that response to high frequency ventilation might predict the need for ECMO. Unfortunately ECMO is not suitable for premature infants, especially for VLBW infants because of increased risk of intracranial hemorrhage (30).

In the responder group, early improvement of oxygenation was observed whereas there was no improvement of oxygenation during HFOV treatment in the non-responder group. Among various respiratory indices, (A-a)DO_2 was the most sensitive parameter in early prediction of responsiveness to HFOV in RDS. (A-a)DO_2 was reduced significantly lower level as early as 2 hr after the start of HFOV treatment compared to the pre-HFOV in the responder group, and it was also significantly lower than in the non-responder group. In Prasertsom's preliminary study, he reported (A-a)DO_2 after HFOV predicted mortality and neurologic outcome.

a/APO_2 was significantly increased immediately after HFOV in both groups. Therefore, a/APO_2 had no predictive value.

OI showed a decreasing tendency after HFOV treatment in the responder group, but had no statistical significance. Because the difference of OI between the two

groups was only observed after 24 hr of HFOV treatment, it had no value in early prediction of responsiveness to HFOV. But some other studies (17, 31) suggested OI or a/APO_2 as a predictor. In term newborn infants and pediatric patients with respiratory failure, a/APO_2 and OI were useful predicting factors for response to HFOV. The exact mechanism why predicting respiratory indices is different according to patient population is unknown. Maybe difference in pulmonary maturity can be considered an important factor.

To be successful, some therapeutic modalities have to be instituted before the development of extensive and irreversible ventilator-induced lung injury. It is very important to identify patients who are at high risk of failure and of death with any of new therapeutic modalities as early as possible. Timely selection of other therapeutic modalities is mandatory for surviving the patients.

With our observation in this study, $(A\text{-}a)DO_2$ was the most and sensitive predictor for respponse to HFOV in VLBW infants with severe RDS failed to improve with CMV. It was possible to predict prognosis exactly as early as 2 hr after HFOV treatment by analyzing the change of $(A\text{-}a)DO_2$ value.

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