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Massive Pulmonary Hemorrhage in Newborn Infants Successfully Treated with High Frequency Oscillatory Ventilation

Massive pulmonary hemorrhage (MPH) in newborn infants is a catastrophic event with a fatal result. The aim of this study was to assess the efficacy of high frequency oscillatory ventilation (HFOV) as a rescue therapy for MPH in newborn infants. Eighteen newborn infants with MPH refractory to conventional mechanical ventilation were treated with HFOV. Changes in oxygenation were assessed using arterial-alveolar oxygen tension ratio (a/APO_2) and oxygenation index (OI) during HFOV. The most common underlying disorder of MPH was preterm patent ductus arteriosus (PDA). Thirteen out of 18 (72%) newborn infants with MPH responded to HFOV and survived. Five out of 18 (28%) did not respond to HFOV and died. There were no differences between responders and nonresponders in gestational age, birth weight, pre-HFOV OI, and age of MPH onset. In responders, there was a rapid increase in a/APO_2 from 0.18 ± 0.04 to 0.40 ± 0.08 at 30 minutes after HFOV. There was also significant decrease in OI from 14.9 ± 4.7 to 8.1 ± 1.5 at 1 hour after HFOV. We conclude that HFOV shows rapid and dramatic improvements and has ultimately life-saving effects in MPH of newborn infants.

Key Words : *Hemorrhage; Infants, newborn; High-frequency ventilation*

Sun Young Ko, Yun Sil Chang, Won Soon Park

Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University, College of Medicine, Seoul, Korea

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Address for correspondence
Won Soon Park, M.D.
Department of Pediatrics, 50 Ilwon-dong, Kangnam-gu, Samsung Medical Center, Sungkyunkwan University, College of Medicine, Seoul 135-230, Korea
Tel : +82.2-3410-3523, Fax : +82.2-3410-0043
E-mail : wspark@smc.samsung.co.kr

INTRODUCTION

Massive pulmonary hemorrhage (MPH) in newborn infants is invariably fatal and its mortality rate goes up to 75-90% (1). Its incidence varies between 1-4/1,000 live-births, and most cases occur in premature or in newborn infants small for their gestational age (2). The common underlying disorders are asphyxia, infection, coagulopathy, and hypothermia (3). Some studies reported that the risk for pulmonary hemorrhage associated with respiratory distress syndrome and surfactant therapy has increased (4-6).

In MPH, accumulation of the hemorrhagic fluid in alveoli forms alveolar diffusion barrier (7). It causes inability of gas exchange and results in acute deterioration with increased ventilatory support. Newborn infants with MPH who need high levels of assisted ventilation requirements are often refractory to conventional mechanical ventilation (CMV) and have a fatal result. They may be substantial morbidity in survivors resulting from secondary lung injury due to barotrauma or volutrauma. Previous studies reported that HFOV was effective in severe respiratory failure refractory to CMV, and decreased the occurrence of chronic lung disease in survivors (8, 9).

The purpose of our study was to determine the efficacy of HFOV as a rescue therapy for MPH refractory to CMV in newborn infants.

MATERIALS AND METHODS

Study population

In our study, 18 newborn infants were included, who had MPH and HFOV treatment and admitted to the NICU of the Samsung Medical Center from December 1994 to March 1997. We reviewed each patient's record to analyse various parameters including epidemiological characteristics, ventilator parameter, arterial blood gases, and respiratory index (arterial-alveolar oxygen tension ratio, oxygenation index). MPH was defined as the presence of blood-stained frothy effluence from the trachea, acute change in the chest X-ray with total opacification of both lungs, and drop in the hematocrit (10).

High frequency oscillatory ventilatory strategy

All patients were initially managed with conventional mechanical ventilators in a time-cycled, pressure-controlled mode (Infant star, Infrasonics Inc. San Diego, CA). HFOV was delivered with a ventilator SensorMedics model 3100 (Critical Care Corp., Yorba Linda, CA.) or Humming V (Metran medical instrument MFG. Co., LTD.). HFOV was provided when severe respiratory failure occurred, as reflected by a/APO_2 (arterial-alveolar oxygen tension ratio) <0.2 and/or oxygenation index (OI) >10, despite the mean air way pressure (MAP) of >10 cm H_2O and 1.0 of FiO_2 of CMV settings.

In HFOV strategy, initial MAP was set at 2-3 cm H_2O above the MAP used on CMV just prior to the beginning of HFOV treatment. MAP was increased by 1 cm H_2O increments until optimal oxygenation and adequate lung recruitment were obtained. Adequate lung recruitment was confirmed by chest radiography which showed evidence of normal lung inflation with the diaphragm level dropping to the eighth or ninth posterior rib level. FiO_2 was set at the same concentration as in CMV.

The initial delta P (amplitude or stroke volume) was selected on the basis of adequate chest wall vibration and was adjusted later by monitoring of arterial CO_2 tension. Ventilator frequency was fixed at 15 Hz. Inspiratory to expiratory time ratio was maintained at 0.33 in SensorMedics.

To wean, FiO_2 was first decreased to less than 0.7, and then FiO_2 and MAP were alternatively decreased (MAP were decreased in 1 cm H_2O increments). The patient was considered to wean to CMV when adequate oxygenation was maintained with less than 0.5 of FiO_2 and 8 cm H_2O of MAP. The MAP decreased whenever chest radiograph showed hyperinflation. A chest radiograph was obtained at 2 hours after HFOV, then obtained when necessary.

Outcomes

Our patients were divided into two groups based on their responses to HFOV. The responder was defined as one who responded to HFOV treatment and survived. The nonresponder was defined as one who could not maintain oxygenation with HFOV treatment and died. OI and a/APO_2 were calculated as $[(Paw \times FiO_2)/PaO_2 \times 100]$ and $[PaO_2/(713 \times FiO_2\text{-}PaCO_2/R)]$. We compared the baseline of OI and a/APO_2 and each measures at 30 min, 1, 2, 6, 12, and 24 hrs after HFOV. Differences between the two groups were analysed using repeated-measures analysis of variance (ANOVA) and student t-test by SAS software ver. 6.04. A $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of patients

We studied 18 newborn infants with MPH. Their mean birth weights and gestational age were 1,583±163 g (709-3,180 g) and 31.8±1.0 weeks (25-41 weeks). The most common underlying disorder was preterm patent ductus arteriosus (PDA) (11/18, 61%), and seven of them had respiratory distress syndrome (RDS) and received surfactant therapy. The underlying disorders were RDS without PDA (4/18, 22%), meconium aspiration syndrome (2/18, 11%), and birth asphyxia (1/18, 6%) (Table 2).

Outcomes

Thirteen out of 18 (13/18, 72%) with MPH responded to HFOV and survived. But 5 infants (5/18, 28%) did not respond to HFOV and died. The birth weight, gestational age, onset of MPH, and pre-HFOV OI did not differ significantly between the two groups (Table 1).

The response rate according to the underlying disorders was shown in Table 2. Most diffuse alveolar diseases

Table 1. Characteristics of patients according to response to HFOV

	Responders (survivor) (n=13)	Nonresponders (death) (n=5)
Gestational age (wk)	32.4±0.9 (27-38)	30.3±2.7 (25-41)
Birth weight (g)	1,644±182 (903-3180)	1,426±371 (709-2800)
Sex (M:F)	7 : 5	3 : 2
OI prior to HFOV	14.9±4.7	9.7±1.5
Duration of HFOV (days)	2.5±0.6 (0.5-8.1)	1.1±0.3 (0.4-1.3)
Age of MPH onset (hours after birth)	76±27 (2-147)	22±7 (7-48)

Values are presented as mean±SE.
HFOV, high frequency oscillatory ventilation; MPH, massive pulmonary hemorrhage; OI, oxygenation index.

Table 2. Response rate of HFOV according to underlying disorders in massive pulmonary hemorrhage of newborn infants

	Responders (n=13)	Nonresponders (n=5)	Response rate (%)
PDA (11)	8	3	73
RDS without PDA (4)	3	1	75
MAS (2)	2	0	100
Birth asphyxia (1)	0	1	0

PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome.

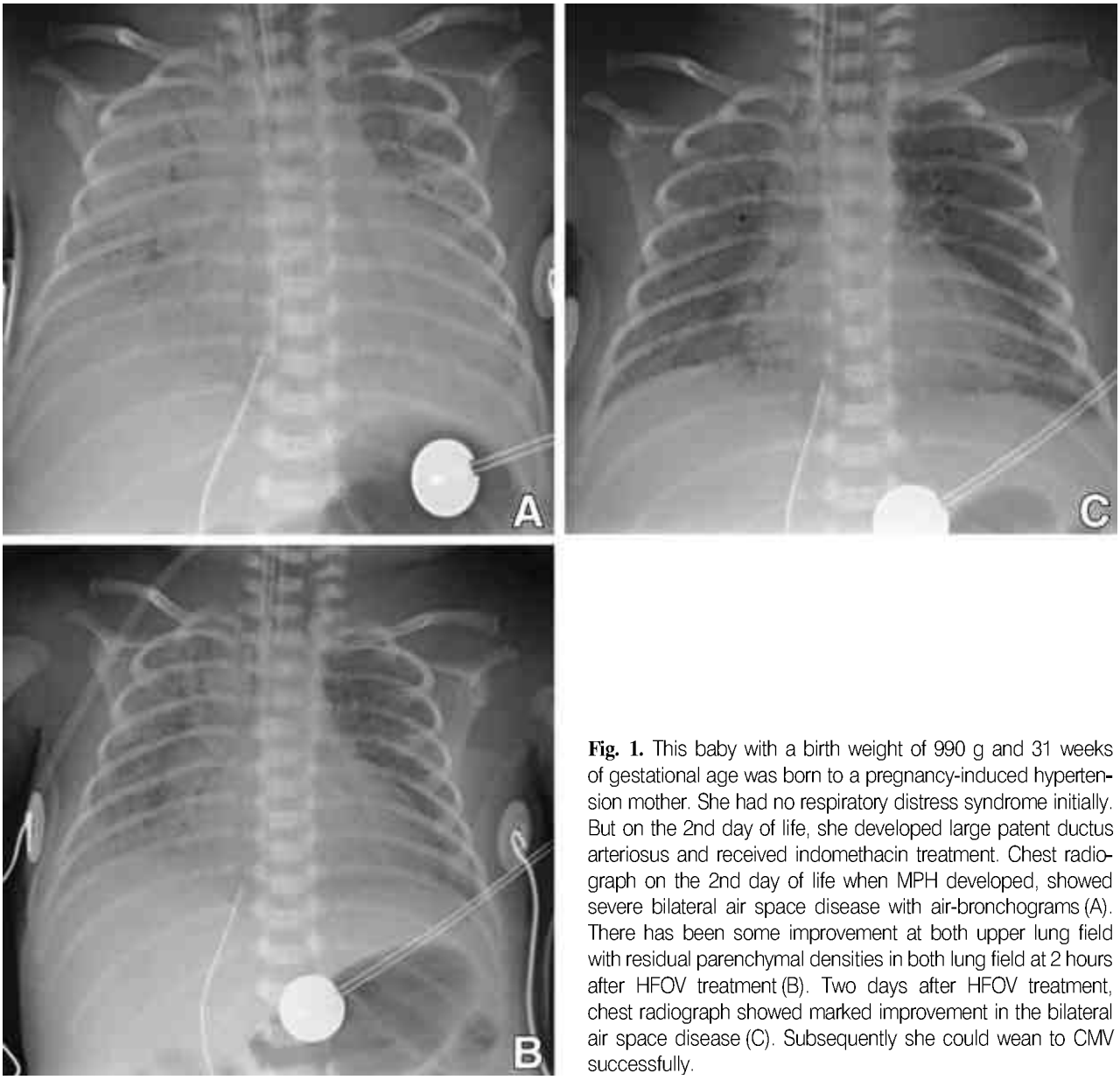

Fig. 1. This baby with a birth weight of 990 g and 31 weeks of gestational age was born to a pregnancy-induced hypertension mother. She had no respiratory distress syndrome initially. But on the 2nd day of life, she developed large patent ductus arteriosus and received indomethacin treatment. Chest radiograph on the 2nd day of life when MPH developed, showed severe bilateral air space disease with air-bronchograms (A). There has been some improvement at both upper lung field with residual parenchymal densities in both lung field at 2 hours after HFOV treatment (B). Two days after HFOV treatment, chest radiograph showed marked improvement in the bilateral air space disease (C). Subsequently she could wean to CMV successfully.

responded well. But birth asphyxia patient did not respond (Table 2).

In responders, a/APO_2 increased at 30 minutes and OI decreased significantly at 1 hour after HFOV therapy (Table 3). Also in responders, there was a rapid improvement in chest radiographic findings (Fig. 1). In nonresponders, however, there were no improvements in OI and a/APO_2 at any time during HFOV therapy (Table 3).

In responders, MAP decreased significantly at 24 hours after HFOV treatment (18.2±1.2 cm H_2O at 30 min to 13.7±1.4 cm H_2O at 24 hr after HFOV). In nonresponders, however, MAP did not decrease during HFOV therapy.

Table 3. OI & a/APO_2 prior to and during HFOV

	Responders (survivor) (n=13)		Nonresponders (death) (n=5)	
	OI	a/APO_2	OI	a/APO_2
pre-HFOV	14.9±4.7	0.18±0.04	9.7±1.5	0.14±0.01
HFOV				
30 min	12.6±3.6	0.40±0.08*	12.7±7.1	0.22±0.09
1 hr	8.1±1.5*	0.36±0.14*	13.9	0.15
2 hr	4.3±2.0*	0.13±0.02	19.2±3.2	0.25±0.08
12 hr	10.6±2.6	0.33±0.04*	17.7±4.7	0.16±0.01
24 hr	7.4±1.2*	0.38±0.05*	12.7±5.0	0.25±0.06

Values are presented as mean±SE.
HFOV, high frequency ventilation; OI, oxygenation index; a/APO_2, arterial-alveolar O_2 tension ratio.
*: $p<0.05$ compared to pre-HFOV.

DISCUSSION

In our study, thirteen of 18 newborn infants with MPH responded to HFOV and survived. Our results suggest that HFOV could be used as a highly efficacious therapeutic modality in MPH of newborn infants.

MPH mostly afflicted low birth weight infants (11). Even if our patients' birth weights were in wide range (903-3,180 g), most of them were low birth weights (16/18, 89%) and premature infants (15/18, 83%).

Since exogenous surfactant was introduced, frequency of MPH in premature RDS has increased significantly (12). In our study, the most common underlying disorder of MPH was PDA associated with prematurity. Majority of them had RDS and received surfactant therapy. It shows that improved pulmonary compliance has an effect on these results which lead to reduced pulmonary vascular resistance (13). Decreased pulmonary vascular resistance can increase pulmonary blood flow and results in an acute rise in lung capillary pressure (14). Therefore in most instances pulmonary hemorrhage is a reflection of advanced pulmonary edema.

Paranka et al. reported a disease-specific response rate in ECMO candidates treated with HFOV (15). Even though there is few data about HFOV treatment in pulmonary hemorrhage, the efficacy of HFOV in idiopathic pulmonary hemorrhage of infancy was reported by Pappas et al. (16). In our clinical trial, those newborn infants who survived showed rapid and dramatic improvements of gas exchange within 1 hr after HFOV treatment.

We employed a ventilatory strategy designed to rapidly recruit and maintain optimal lung volume, the so-called "high-volume strategy" (17). As our data demonstrate, this approach produced rapid improvements in oxygenation and radiographic findings with increase in MAP. In responders, MAP also significantly decreased at 1 day after HFOV. In general, responders received HFOV treatment for about 2.5 days, and were successfully weaned from HFOV within 3 days.

Age of MPH onset in our patients was of various range (2-147 hrs after birth). Thirteen out of 18 newborn infants had MPH within 48 hrs after their birth. All deaths of MPH newborn infants occurred within 48 hrs. It seemed to have different responses depending on age of MPH onset although it is not significant statistically. We think that this may be due to the severity of the underlying disorder and unstable conditions of newborn infants right after birth.

We would like to analyse the causes of death in our study. The newborn infants with asphyxia had multiple organ failure. They usually suffered from acute left ventricular failure which is caused by hypoxia and acidosis. This causes an increase in pulmonary capillary pressure with rapid evolution of hemorrhagic edema fluid into the air spaces (18). Our birth asphyxia patient developed airleak syndrome during HFOV therapy. The airleak syndrome may aggravate this patient's condition and lead to cardiopulmonary instability. In general, HFOV is a relative contraindication in hypotensive shock state such as birth asphyxia. Therefore, patients with cardiovascular instability requires careful assessment in HFOV treatment. Our birth asphyxia patient also had a seizure attack. So we think that his cardiovascular compromise may be due to a central nervous system dysfunction as well as airleak syndrome. The other two nonresponders had RDS and also developed airleak syndrome. To manage these patients with diffuse alveolar lung disease and airleak syndrome, we first had to decide what is the prominent problem. For those who had severe airleak syndrome as a primary problem, we used the lowest MAP that will allow adequate gas exchange. Unfortunately our patients' underlying lung conditions required high MAP, so they could not maintain oxygenation with the above strategy and rapidly progressed to cardiopulmonary arrest due to airleak itself.

Another two nonresponders had disseminated intravascular coagulopathy (DIC). While most pulmonary hemorrhages are reflection of advanced pulmonary edema, our cases of two nonresponders represented true hemorrhages, although we did not check hemoglobin in the pulmonary effluent. Their MPH did not cease and hemoglobin level in blood dropped rapidly. We think that in these cases the above mechanism may be involved. As long as their underlying conditions causing hemorrhage were not improved, HFOV could not help them to recover from MPH and they deteriorated rapidly.

In conclusion, about 72% patients showed rapid and dramatic improvements with HFOV therapy and survived in our study. We determine that HFOV is a safe and effective rescue treatment modality in MPH of newborn infants.

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REFERENCES

1. Avery GB, Fletcher MA, MacDonald MG. *Neonatology. 4th eds. Philadelphia: J.B. Lippincott Company, 1994: 450.*
2. Fekete M, Nemeth A. *Neonatal pulmonary hemorrhage, birthweight, gestational age and intrauterine growth. Acta Pediatrica Hungarica 1985; 26: 65-71.*
3. Fedrick J. *Certain causes of neonatal death IV. Massive pul-*

monary hemorrhage. Biol Neonate 1971; 18: 243.

4. Fujiwara T, Maeta H, Chida S. *Artificial surfactant therapy in hyaline membrane disease. Lancet 1991; 338: 1127-30.*
5. Van Houten J, Long W, Mullett M. *Pulmonary hemorrhage in premature infants after treatment with synthetic surfactant: an autopsy evaluation. J Pediatr 1992; 120: S40.*
6. Rogers D. *Pulmonary hemorrhage surfactant & low birth weight babies (Letter). Lancet 1993; 341: 698.*
7. Rice TB, Torres A. *Pneumonitis and interstitial disease. In: Fuhrman BP, Zimmerman JJ, eds. Pediatric critical care. St. Louis: Mosby Yearbook, 1992: 481-4.*
8. Clark RH, Gerstmann DR, Null DM Jr. *Prospective randomized comparison of high frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992; 89: 5-12.*
9. HiFO study group. *Randomized study of high frequency oscillatory ventilation in infants with severe respiratory distress syndrome. J Pediatr 1993; 122: 609-19.*
10. Bomsel F. *Radiologic diagnosis of massive pulmonary hemorrhage of the newborn. Ann Radiol (Paris) 1975; 18: 419-30.*
11. Saidan M, Hifzi I, Khan M. *Pulmonary hemorrhage in low birth weight babies. Lancet 1993; 341: 120.*
12. Raju TNK, Langenberg P. *Pulmonary hemorrhage and exogenous surfactant. A metaanalysis. J Pediatr 1993; 123: 603-10.*
13. Kaapa P, Seppanen M, Kero P, Saraste M. *Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. J Pediatr 1993; 123: 115-9.*
14. Clyman RI, Jobe A, Heymann M, Ikegami M, Roman C, Payne B, Mauray F. *Increased shunt through the patent ductus after surfactant replacement therapy. J Pediatr 1982; 100: 101-7.*
15. Paranka MS, Yoder BA, Clark RH. *Predictors of failure of high frequency oscillatory ventilation in term infants with severe respiratory failure. Pediatrics 1995; 95: 400-4.*
16. Pappas MD, Sarnaik AP, Meert KL, Hasan RA, Lieh-Lai MW. *Idiopathic pulmonary hemorrhage in infancy. Clinical features and management with high frequency ventilation. Chest 1996; 110: 553-5.*
17. McCulloch PR, Forkert PG, Froese AB. *Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant deficient rabbits. Am Rev Respir Dis 1988; 137: 1185-92.*
18. Cole VA, Normand ICS, Reynolds EOR, Rivers RPA. *Pathogenesis of hemorrhagic edema and massive pulmonary hemorrhage in the newborn. Pediatrics 1973; 51: 175-87.*