HIGH FREQUENCY OSCILLATORY VENTILATION IN NEWBORNS WITH IDIOPATHIC PERSISTENT PULMONARY HYPERTENSION

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ABSTRACT

Three consecutive term infants diagnosed as suffering from idiopathic persistent pulmonary hypertension of the newborn (PPHN) were tried on high frequency oscillatory ventilation (HFOV) after failure of conventional mechanical ventilation (CMV). All experienced a significant improvement in oxygenation. All three infants survived. HFOV was utilised in a fourth term infant initially diagnosed as having idiopathic PPHN with an immediate benefit. This infant subsequently died and was found at autopsy to have a lethal congenital maldevelopment of pulmonary microcirculation. No serious adverse effects were encountered with HFOV in contrast to the use of pharmacologic agents where hypotension was a serious problem. A therapeutic trial of HFOV is simple and efficient, and would not cause undue delay in the commencement of other rescue therapy should it prove unsuccessful. We predict HFOV will replace non-specific vasoactive agents as the standard first line alternative to CMV for the treatment of idiopathic PPHN.

Keywords: *high frequency oscillatory ventilation, idiopathic persistent hypertension of the newborn.*

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) occurs in the early postnatal period and is characterised by persistent right to left shunt through foetal channels causing severe hypoxaemia. It is a life-threatening condition and is reportedly the commonest cause of death for infants above 1,000g without lethal congenital malformation in European neonatal centres[1]. The estimated incidence is 1 in 1,400 livebirths and it is responsible for 3.9% of neonatal admissions in the United States[2]. Although PPHN is commonly associated with acquired neonatal conditions such as birth asphyxia, meconium aspiration syndrome and septicaemia, a significant proportion of cases are idiopathic in origin. Despite early identification, aggressive conventional ventilatory and pharmacologic therapies, mortality and morbidity associated with PPHN remain high. We have successfully used high frequency oscillatory ventilation (HFOV) for the treatment of 3 consecutive cases of idiopathic PPHN in the past 12 months and report our experience with this new modality of treatment.

PATIENTS

Three consecutive term babies diagnosed as suffering from idiopathic PPHN were admitted to the neonatal unit between the period of June 93 to May 94. Their demographic data are summarised in Table I and ventilator settings with blood gas measurements in Tables II to V. Echocardiography was performed in all cases and confirmed an anatomically normal heart with right to left shunt at the atrial and/or ductal levels. Life-threatening infection was excluded by negative cerebrospinal fluid, blood, urine and tracheal aspirate cultures and persistently normal C-reactive protein. HFOV was tried when the infants either failed to respond to conventional mechanical ventilation (CMV) or the clinical condition remained static on prolonged CMV. Two types of high frequency oscillatory ventilator were used depending on availability. They were the SensorMedics 3100A (SensorMedics, Inc., Anaheim, Calif.) and the Infantstar (Infrasonic Inc., Calif.). The initial settings of HFOV were as follows: frequency 15 Hz (900 breaths per minute); inspiratory to expiratory (I:E) ratio 1:2; fractional inspired oxygen (FiO_2) unchanged; mean airway pressure ($Pa\bar{w}$) 2 to 4 cm H_2O greater than that used for CMV at the time of changeover and a pressure amplitude that produced visible chest wall vibration. The optimal $Pa\bar{w}$ was achieved by frequent and small stepwise increments of the mean airway pressure until

Table I - Clinical features of the 4 infants with PPHN

	Patient A	Patient B	Patient C	Patient D
Gestational age (weeks)	39	41	37	41
Birthweight (G)	2900	2610	2350	3700
Apgar scores				
1 minute	9	7	9	9
5 minutes	10	6	10	9
Sex	F	F	F	M
Mode of delivery	vaginal	vaginal	Caesarean section	vaginal
Non-lethal congenital anomalies	Nil	Nil	Nil	Imperforate anus
Duration of CMV before HFOV (hours)	238	4	20	16
Duration of HFOV (hours)	151	39	68	35
Duration of O_2 dependency (days)	23	9	10	-
Outcome	Alive	Alive	Alive	Died

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preductal oxygen saturation and oxygen tension in arterial blood were above 95% and 10 Kpa respectively. No infant showed radiographic evidence of lung hyperinflation or developed significant hypotension after changeover to HFOV. All survivors were weaned and then changed to low pressure slow rate CMV for the purpose of extubation. Cranial ultrasound scans on discharge were normal. No neurodevelopmental or pulmonary sequelae were detectable when reviewed at 3 to 6 months of age. Their clinical courses are described individually.

Case A

Infant A developed respiratory distress with tachypnoea and cyanosis shortly after birth and required intermittent positive pressure ventilation (IPPV) at 9 hours of age. The initial ventilator settings were peak inspired pressure (PIP) 26cmH_2O. I:E ratio 1:1 and FiO_2 0.80. Chest radiograph was normal. She continued to be hypoxaemic and ventilation was increased to PIP 38cmH_2O, I:E ratio 2:1, and FiO_2 1.0 at the age of 13 hours. Tolazoline infusion (2mg/kg/hour after 2mg/kg loading) was commenced at the same time until day 5 when it was replaced by prostacyclin infusion (80ng/kg/min). Multiple infusions of plasma and inotropic support with dopamine (15mcg/kg/min) and dobutamine (15 mcg/kg/min) were required to maintain an adequate blood pressure (ie mean blood pressure ≥ 40mmHg) during treatment with vasodilating agents. Due to lack of progress in ventilation and oxygenation, HFOV (Infantstar) was started on day 10. It produced a steady increase in oxygenation (Fig 1, Table II) and allowed gradual weaning of ventilation to successful extubation on day 17. All vasoactive agents could be discontinued within 4 hours of commencement of HFOV.

Fig 1 – Arterial oxygen tension before and after HFOV

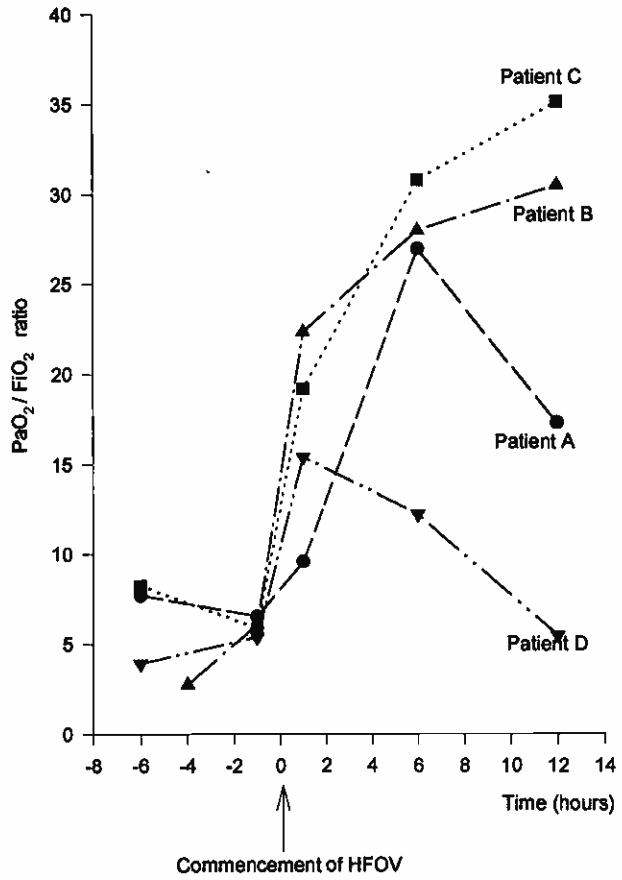

Table II - Ventilation data before and after HFOV for Infant A

	Before HFOV		After commencing HFOV				
	4-6 hours	1 hour	1 hour	6 hours	12 hours	48hours	72 hours
Mode of ventilation	CMV	CMV	HFOV	HFOV	HFOV	HFOV	HFOV
pH	7.48	7.49	7.31	7.39	7.46	7.41	7.37
PaO_2 (Kpa)	7.33	6.56	9.1	25.6	15.6	13.7	10.93
$PaCO_2$ (Kpa)	2.98	3.28	6.35	4.97	3.70	5.31	5.70
PIP (cmH_2O)	38	38	–	–	–	–	–
$Pa\bar{w}$ (cmH_2O)	18	18	20	20	18	13	10
Amplitude	–	–	35	36	36	30	26
FiO_2	0.95	1.0	0.95	0.95	0.90	0.65	0.55
Oxygenation Index	31	37	28	10	14	8	7

Case B

Infant B developed severe respiratory distress within the first hour of life requiring IPPV. Chest radiograph after intubation showed oligaemic lung fields. Her ventilatory requirement progressively increased and by the second hour of life, she was requiring a PIP of 34cmH_2O and FiO_2 1.0. She suddenly became bradycardic and a repeat chest radiograph showed a left-sided pneumothorax. Despite successful drainage she remained profoundly hypoxaemic. A test dose of tolazoline (2mg/kg) had no effect on oxygenation and significantly dropped her blood pressure. Plasma volume expansion and inotropic support with dopamine (15mcg/kg/min) and dobutamine (10mcg/kg/min) were required to restore a satisfactory blood pressure. Failing CMV, she was commenced on HFOV (Infant star) at 4 hours of age with almost immediate improvement in oxygenation (Fig 1, Table III). No further hypoxic episode was encountered. HFOV requirement decreased over the next 2 days and she was extubated on day 4.

Table III - Ventilation data before and after HFOV for Infant B

	Before HFOV		After commencing HFOV				
	4-6 hours	1 hour	1 hour	6 hours	12 hours	48hours	72 hours
Mode of ventilation	CMV	CMV	HFOV	HFOV	HFOV	CMV	Headbox
pH	7.56	7.67	7.50	7.50	7.47	7.451	7.39
PaO_2 (Kpa)	2.73	6.1	19.0	18.2	24.4	10.32	12.7
$PaCO_2$ (Kpa)	2.70	1.77	3.78	4.78	4.82	4.65	4.61
PIP (cmH_2O)	34	34	–	–	–	18	–
$Pa\bar{w}$ (cmH_2O)	14	14	15	15	15	7	–
Amplitude	–	–	30	35	30	–	–
FiO_2	1.0	1.0	0.85	0.65	0.80	0.30	0.35
Oxygenation index	68	31	9	7	7	3	–

Case C

Infant C developed severe respiratory distress shortly after birth and required IPPV at 5 hours of age with moderate ventilatory settings of PIP 23cmH_2O, I:E ratio 1:1 and FiO_2 0.55. Chest radiograph showed oligaemic lung fields. At 25 hours of age, despite increasing ventilation to a PIP 26cmH_2O and FiO_2 1.0, she remained hypoxaemic and was commenced on HFOV (Sensormedics 3100A). Improvement of oxygenation was again dramatic (Fig 1, Table IV) and

sustained, allowing extubation on day 5. Vasodilator therapy was never given and she did not require inotropic support for maintenance of blood pressure.

Table IV - Ventilation data before and after HFOV for Infant C

	Before HFOV		After commencing HFOV				
	4-6 hours	1 hour	1 hour	6 hours	12 hours	48hours	72 hours
Mode of ventilation	CMV	CMV	HFOV	HFOV	HFOV	HFOV	HFOV
pH	7.35	7.33	7.29	7.46	7.48	7.47	7.42
PaO_2 (Kpa)	7.42	5.90	19.2	27.7	30.9	19.6	14.8
$PaCO_2$ (Kpa)	5.76	6.20	6.41	5.47	4.39	5.06	5.12
PIP (cmH_2O)	26	26	–	–	–	–	–
$\bar{Paw}$ (cmH_2O)	13	13	19	19	19	15.5	6
Amplitude	–	–	50	45	45	35	35
FiO_2	0.90	1.0	1.0	0.9	0.88	0.45	0.40
Oxygenation index	21	29	13	8	7	5	2

Table V - Ventilation data before and after HFOV for Infant D

	Before HFOV		After commencing HFOV				
	4-6 hours	1 hour	1 hour	6 hours	12 hours	48hours	72 hours
Mode of ventilation	CMV	CMV	HFOV	HFOV	HFOV	–	–
pH	7.58	7.70	7.33	7.31	7.41	(patient deceased)	–
PaO_2 ((Kpa)	3.92	5.40	15.40	12.20	5.50	–	–
$PaCO_2$ (Kpa)	2.79	1.32	5.30	4.10	3.47	–	–
PIP (cmH_2O)	42	42	–	–	–	–	–
$\bar{Paw}$ (cmH_2O)	21	21	24	24	24	–	–
Amplitude	–	–	42	41	44	–	–
FiO_2	1.0	1.0	1.0	1.0	1.0	–	–
Oxygenation index	71	52	21	26	58	–	–

Case D

A fourth case is described to illustrate the use of HFOV, although the infant ultimately failed HFOV because of a rare and lethal congenital maldevelopment of pulmonary microcirculation[3-6]. Infant D had no respiratory distress at birth but developed tachypnoea, chest retractions and cyanosis requiring IPPV at 3 hours of age. The initial ventilatory requirement was PIP 28cmH_2O, I:E ratio 1:1 and FiO_2 0.90. Chest radiograph showed non-specific diffuse haziness. Despite aggressive escalation of CMV to a maximum PIP 42cmH_2O, reversed I:E ratio 2.5:1 and FiO_2 1.0 at 16 hours of age, he continued to experience frequent episodes of severe and prolonged desaturation. Therapies directed towards lowering the pulmonary vascular resistance included alkalinisation of blood pH to 7.5 with hyperventilation and bicarbonate infusion, tolazoline infusion (2mg/kg/hour after 2mg/kg loading dose), prostacyclin infusion (120ng/kg/min) and $MgSO_4$ infusion (50mg/kg/hour after 200mg/kg loading dose). Episodes of severe hypotension necessitating plasma expansion and inotropic support were experienced after the introduction of these vasodilating agents. None of the manoeuvres resulted in sustained improvement in oxygenation. He was commenced on HFOV (SensorMedics 3100A) at 19 hours of age with rapid and significant improvement in oxygenation (Fig 1, Table V). This initial period of HFOV represented the most stable time of his clinical course. The episodes of hypoxaemia subsequently recurred 6 hours later despite HFOV, continuation of prostacyclin, $MgSO_4$ and inotropic infusions. He became increasingly refractory to treatment and died on day 3. Postmortem examination revealed the unexpected diagnosis of congenital alveolar capillary dysplasia.

DISCUSSION

The past decade has witnessed many new treatments that have revolutionised the management of respiratory failure in the newborn[7]. Those described include: extracorporeal membrane oxygenation (ECMO); the latest generation of vasodilating agents eg nitric oxide, magnesium sulphate; and new methods of ventilation including the use of volume cycled ventilation, high frequency jet ventilation, HFOV and liquid ventilation. Many such therapies are available only at specialised centres and are still considered experimental. In recent years, high frequency ventilation has been the focus of attention for treatment of respiratory failure for both term[8-11] and preterm infants[12-15]. HFOV, in particular, appears to be an effective rescue technique in term infants who fail to respond to CMV and allows successful management of patients who meet the ECMO criteria but without needing to resort to ECMO[9-11]. In the 4 articles which reported the efficacy of HFOV in term infants with severe PPHN[8-11], all comprised a heterogenous population with a wide variation of diagnoses.

In our report, we have demonstrated that HFOV facilitated gaseous exchange in infants who failed CMV. Improvement in oxygenation was almost instantaneous once the optimal $\bar{Paw}$ was achieved. All three cases of idiopathic PPHN survived. The non-survivor was subsequently found at postmortem to have a lethal congenital condition of pulmonary microcirculation maldevelopment[3-6]. Even this patient showed a dramatic but short-lived improvement in oxygenation with HFOV. The mechanism giving rise to improvement in oxygenation remains speculative. Hypoxaemia during CMV was not the result of overinflation of the lungs with impairment of venous return as the chest radiographs did not show pulmonary hyperinflation before or after switching over to HFOV. Nor were any significant fluctuations in blood pressure observed during this time. Moreover, the immediate improvement in oxygenation could not be explained by producing hypocarbia as suggested by Kohelet et al[8], since patients A, C and D all had lower $PaCO_2$ levels on CMV before HFOV was commenced. A higher $\bar{Paw}$ might have achieved better alveolar recruitment to account for the favourable response to HFOV[9]. In addition, by keeping a near constant $\bar{Paw}$ with HFOV and avoiding the phasic, large amplitude pressure and volume changes induced by each cycle of CMV, the pattern of lung inflation is stabilised[13]. Consequently, regional hyperinflation and alveolar or airway collapse should be minimised and more even distribution of gas within the lung achieved[13].

No adverse effects associated with HFOV such as necrotising tracheobronchitis, pulmonary air leak syndrome, bronchopulmonary dysplasia and intracranial haemorrhage were seen in our patients. Severe hypotension occurred in each case where vasodilating agents were used but was not observed during HFOV despite the use of higher $\bar{Paw}$.

ECMO has been successfully used for neonates dying of acute respiratory failure but its efficacy and safety have been questioned when compared to less invasive conventional therapy[16,17]. Recent studies have suggested that HFOV

improves oxygenation and reduces the demand for ECMO without increasing morbidity[8-11]. Up to sixty percent of neonates with severe PPHN who failed CMV and fulfilled the criteria for ECMO treatment were successfully managed with HFOV and avoided ECMO[10,11]. ECMO remains a costly, centre specific, invasive procedure open to serious technical problems and carrying a significant risk of major complication including ligation of major vessels with disturbances in cerebral blood flow, thromboembolism and bleeding[9,10]. A therapeutic trial of HFOV is simple and efficient, and would not cause undue delay in the commencement of other rescue therapy should it prove unsuccessful. The role of nitric oxide, if available, would be complementary to this strategy.

We conclude that HFOV provides effective ventilation and rapid improvement of oxygenation in neonates suffering from idiopathic PPHN who have not responded to conventional ventilation. It is relatively safe and well tolerated, especially when compared to vasodilator therapy and ECMO. We predict HFOV, with or without nitric oxide, will soon replace non-specific vasodilating agents as the standard first line alternative to CMV for the treatment of idiopathic PPHN and should be tried before resorting to ECMO or other invasive therapies.

References

1. Roberton NRC. Persistent fetal circulation complicating other neonatal lung disorders - definition and diagnosis. In: Clinch J, Matthews T, ed. Perinatal medicine. Lancaster: MTP Press, 1985: 181-7.
2. Weigel TJ, Hageman JR. National survey of diagnosis and management of persistent pulmonary hypertension of the newborn. J Perinatol 1990; 10:369-75.
3. Janney CG, Askin FB, Kuhn C III. Congenital alveolar capillary dysplasia - an unusual cause of respiratory distress in the newborn. Am J Clin Pathol 1981; 76:722-7.
4. Wagenvoort CA. Misalignment of lung vessels: a syndrome causing persistent neonatal pulmonary hypertension. Hum Pathol 1986; 17:727-30.
5. Cater G, Thibeault DW, Beatty EC, Kilbride HW, Huntrakoon M. Misalignment of lung vessels and alveolar capillary dysplasia: A cause of persistent pulmonary hypertension. J Pediatr 1989; 114:293-300.
6. Abdallah HI, Karmazin N, Marks LA. Late presentation of misalignment of lung vessels with alveolar capillary dysplasia. Crit Care Med 1993; 21:628-30.
7. Donn SM. Alternatives to ECMO. Arch Dis Child 1994; 70:F81-F83.
8. Kohelet D, Perlman M, Kirpalani H, Hanna G, Koren G. High frequency oscillation in the rescue of infants with persistent pulmonary hypertension. Crit Care Med 1988; 16:510-6.
9. Carter JM, Gerstmann DR, Clark RH, Snyder G, Cornish JD, Null Jr DM, et al. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990; 85:159-64.
10. Varnholt V, Lasch P, Suske G, Kachel W, Brands W. High frequency oscillatory ventilation and extracorporeal membrane oxygenation in severe persistent pulmonary hypertension of the newborn. Eur J Pediatr 1992; 151:769-74.
11. Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994; 124:447-54.
12. The HIFI Study Group. High-frequency oscillatory compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989; 320:88-93.
13. Clark RH, Gerstmann DR, Null Jr DM, deLemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992; 89:5-12.
14. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K, et al. A multicenter randomized trial of high frequency oscillatory ventilation as compared with convetional mechanical ventilation in preterm infants with respiratory failure. Early Hum Dev 1993; 32:1-10.
15. HiFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. J Pediatr 1994; 122:609-19.
16. Dworetz AR, Moya FR, Sabo B. Survival in infants with persistent pulmonary hypertension (PPHTN) without extracorporeal membrane oxygenation (ECMO). Pediatr Res 1987; 21:360A.
17. Wung JT, James LS, Kilchewsky E. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. Pediatrics 1985; 76:488-94.