

A Retrospective Study of Infants with Severe Persistent Pulmonary Hypertension (PPHN) Managed without Extracorporeal Membrane Oxygenation (ECMO)

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Abstract

We studied 13 consecutive infants admitted to our Neonatal Intensive Care Unit over 37 months from 1 June 1994 to 30 June 1997, who were diagnosed with severe persistent pulmonary hypertension (PPHN) meeting extracorporeal membrane oxygenation (ECMO) criteria as defined by Bartlett and/or Short. They were managed with conservative ventilation strategy, with emphasis on the use of moderate ventilatory pressures whilst avoiding paralysis. Peak inspiratory pressure (PIP) on intermittent mandatory ventilation was adjusted according to adequate chest excursion. High PIP was avoided. Two main ventilatory techniques were used: 1) low ventilatory rate $\leq 40/\text{min}$, PIP 20 to 30 cmH_2O , inspiratory time (IT) 0.5 seconds, positive end-expiratory pressure (PEEP) 5 cmH_2O , and 2) high ventilatory rate 100/ min , PEEP 0 cmH_2O , IT 0.3 seconds. The aim was to keep preductal $\text{PaO}_2 \geq 50 \text{ mmHg}$. We did not sought to achieve alkalotic pH or low PaCO_2 . When PIP requirements exceeded 30 to 35 cmH_2O , the use of an alternative rescue therapy such as pulmonary vasodilator, high frequency ventilation and/or surfactant were considered. Only 1 infant died of PPHN. Low mortality due to PPHN can be achieved using this strategy. There is a need for a randomised controlled trial to compare this strategy with other alternative treatment strategies.

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Introduction

Persistent pulmonary hypertension (PPHN) is an important cause of neonatal mortality amongst infants who are of term or post-term gestation.^{1,2} The most severely ill of these infants would meet the criteria for the use of extracorporeal membrane oxygenation (ECMO). Indices of severity of illness have been developed by various authors* to predict a high probability of mortality without ECMO intervention. Nevertheless ECMO facilities are only available in a few centres worldwide. It is an invasive, and expensive modality of treatment, and concerns remain regarding the long-term neurodevelopmental outcome of ECMO survivors.³

The optimum management of infants with PPHN is still controversial. In particular there is a lack of consensus with regards to the ventilatory strategy to be employed. Two main strategies are advocated—hyperventilation² and conservative ventilation.⁴

Materials and Methods

We studied 13 consecutive infants admitted to our Neonatal Intensive Care Unit (I / Blue) from 1 June 1994

to 30 June 1997, with severe PPHN meeting ECMO criteria. They were managed with conservative ventilation strategy, with emphasis on the use of moderate ventilatory pressures, whilst avoiding paralysis. When ventilatory pressure requirements were high, the use of pulmonary vasodilators, surfactant and/or high frequency ventilation was considered.

Infants meeting the following entry criteria were studied:

- 1) inborn infants,
- 2) birth weight $\geq 2 \text{ kg}$,
- 3) diagnosed with PPHN as defined below, and
- 4) meeting ECMO criteria as defined by Bartlett et al⁵ and/or Short et al.⁶

Diagnosis of PPHN was based on 1 or more of these 3 criteria:

- 1) two-dimensional echocardiographic evidence of right to left shunt, either at atrial level or at the level of the patent ductus arteriosus;¹
- 2) pre- postductal SaO_2 difference exceeding 5% or PaO_2 difference of $\geq 15 \text{ mmHg}$;³ and
- 3) clinical lability* with echocardiographic evidence of high pulmonary pressure.

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ECMO criteria based on Bartlett et al:⁵

- 1) $\text{PaO}_2 < 40 \text{ mmHg}$ or $\text{pH} < 7.15$ for 2 hours, or
- 2) two of the following for at least 3 hours: $\text{PaO}_2 < 55 \text{ mmHg}$, $\text{pH} < 7.4$, hypotension; or
- 3) four of 7 indicators of barotrauma occurring simultaneously: interstitial emphysema, pneumothorax, pneumoperitoneum, pneumopericardium, subcutaneous emphysema, persistent air leak for 24 hours, mean airway pressure $> 15 \text{ cmH}_2\text{O}$. Two other criteria, diaphragmatic hernia (no cases) and new-born pulmonary insufficiency index, were not used in this study.⁷

ECMO criteria based on Short et al:⁶

- 1) $\text{AaDO}_2 \geq 2610$ for 8 hours, or
- 2) $\text{AaDO}_2 \geq 605$ with peak inspiratory pressure (PIP) $\geq 38 \text{ cmH}_2\text{O}$ for 4 hours.

Treatment Strategy

Conservative ventilatory strategy⁴ was used. Two ventilatory techniques were used in this strategy:

1. Low ventilatory rates (20 to 40 per min), PIP 20 to 30 cmH_2O based on adequate chest excursion and positive end-expiratory pressure (PEEP) 5 cmH_2O , inspiratory time (IT) 0.5 seconds. All infants were initiated on this technique.
2. High ventilatory rates (100/min), PEEP 0, IT 0.3 seconds; PIP was decreased by 3 to 5 cmH_2O compared to PIP whilst on low ventilatory rate strategy. The indication for use of the high ventilatory rate strategy is when $\text{PaO}_2 \leq 50 \text{ mmHg}$ on low ventilatory rate, or PIP requirements exceed 30 to 35 cmH_2O . The goal of treatment was to achieve $\text{PaO}_2 \geq 50 \text{ mmHg}$ whilst avoiding high ventilatory pressure (PIP). Low PaCO_2 or alkalosis was not an objective of treatment. We stressed the use of moderate ventilatory pressures based on adequate chest excursion. High PIP which gave excessive chest excursion and which clinicians used if they wish to achieve low PaCO_2 and respiratory alkalosis was avoided. If the infant responded to the high ventilatory rate (100/min), they were kept on this ventilatory rate. As they improved, PIP was gradually decreased until 20 cmH_2O and ventilator rate would then be decreased.

When PIP requirements exceed 30 to 35 cmH_2O , other alternative rescue strategies were considered. These included:

1. Use of pulmonary vasodilator: We used tolazoline (test dose 1 mg/kg) followed by continuous infusion of 1 mg/kg/h if there was a positive response to the test dose. Also intravenous magnesium sulphate (MgSO_4) had been used. The dose of intravenous MgSO_4 is 200 mg/kg loading dose over 20 to 30 minutes followed by continuous infusion at a rate of 20 to 50 mg/kg/h. The vasodilator is given over the

upper limb or scalp veins.

2. High frequency ventilation: We have in our unit during this study period the Infant Star[®] ventilator which was adapted to provide high frequency interruptor ventilation.
3. Surfactant: This is considered when the diagnosis is hyaline membrane disease or severe meconium aspiration syndrome (MAS). Survanta[®] is used.

Results

There were 13 cases of severe PPHN meeting ECMO criteria as defined by Bartlett et al⁵ and/or Short et al.⁶

Demographic data and characteristics of these infants are shown in Table I. The mean birth weight of the patients was $2871 \pm 481 \text{ g}$ and their mean gestational age at birth was 38.2 ± 2.4 weeks. Their mean Apgar scores were 6.2 ± 2.9 and 7.5 ± 2.0 at 1 and 5 minutes, respectively. The mean first arterial pH was 7.065 ± 0.287 . Ten of the 13 patients satisfied both Bartlett et al⁵ and Short et al⁶ ECMO criteria, while 2 patients satisfied Short et al but not Bartlett et al criteria and 1 patient satisfied only Bartlett et al criteria.

The treatment variables are shown in Table II. The mean duration of ventilatory support (IMV) was 10.6 ± 7.2 days (range 1.5 to 21.0 days). One infant who died from PPHN was ventilated for 1.5 days. The mean maximum PIP was $36 \pm 7 \text{ cmH}_2\text{O}$; all 13 infants had a trial of high ventilatory rates (100/min) but only 9 infants responded. High frequency ventilation was used in 4 patients with good response in only 1 of them. Inotropic support was needed in all of our patients; 1 required only dopamine while the other 12 required both dopamine and dobutamine. Tolazoline, intravenous magnesium sulphate and surfactant were used in 62%, 54% and 23% of the patients, respectively. No patient was paralysed and all except 2 of the patients were sedated using intravenous phenobarbitone.

The outcome data are shown in Table III. Only 1 of the 13 infants died of PPHN. Three (23%) infants had oxygen dependency beyond 28 days of life.

Discussion

This study describes our experience in the management of infants with severe PPHN meeting ECMO criteria. Only 1 of the 13 infants died of PPHN despite the severity of the illness.

Bartlett et al⁵ and Short et al⁶ predicted high mortality in these infants (80% or more) without the use of ECMO. In our discussion of this conservative treatment strategy, we would like to focus on 3 aspects of treatment:

- 1) ventilatory strategy,
- 2) use of alternative "rescue" strategies, and
- 3) paralysis.

TABLE I: MEDICAL DEMOGRAPHIC DATA AND CHARACTERISTICS

S/N	Birth weight (g)	Gestational age (weeks)	Sex†	Race‡	Underlying diagnosis**	Apgar at 1 min	Apgar at 5 min	1st Arterial pH	Maximum AaDO ₂ *	ECMO (Barlett et al ⁵)	ECMO (Short et al ⁶)
1	2830	40	M	C	Primary PPHN	9	9	7.237	634	Yes	Yes
2	3713	40	M	I	MAS	4	7	7.358	638	Yes	Yes
3	2280	36	F	M	Pneumonia	7	9	7.199	>610	Yes	Yes
4	2305	35	M	C	MAS	2	8	7.213	643	Yes	Yes
5	3178	35	M	C	Pneumonia	2	4	7.380	>610	Yes	Yes
6	3400	39	F	C	Perinatal asphyxia	8	8	6.486	644	Yes	Yes
7	2440	40	F	M	MAS	5	7	7.020	637	No	Yes
8	2470	34	M	C	Pneumonia	9	9	6.918	626	Yes	Yes
9	3000	38	M	M	Perinatal asphyxia	9	9	7.119	>610	Yes	Yes
10	3600	41	M	C	MAS	6	7	6.68 1	637	Yes	Yes
11	2592	40	M	M	MAS	9	9	7.430	631	No	Yes
12	264 1	40	F	M	MAS	2	3	7.041	632	Yes	No
13	2880	39	M	M	Perinatal asphyxia	9	9	6.760	657	Yes	Yes

† M: Male, F: Female ‡ C: Chinese, M: Malay, I: Indian

** PPHN: persistent pulmonary hypertension of newborn, MAS: meconium aspiration syndrome

* Maximum AaDO₂ whilst on FiO₂ = 1.0

TABLE II: TREATMENT VARIABLES

S/N	Ventilation days	Max PIP (mmHg)	Max rate (per min)	Response to high ventilatory rates	High frequency ventilation	Tolazoline	Magnesium sulphate	Surfactant	Paralysis	Ionotropes*
1	9	39	100	Yes	No	Yes	No	No	No	Dopa, Dobut
2	9	40	100	Yes	Yes (responded)	Yes	No	No	No	Dopa, Dobut
3	13	41	100	Yes	No	Yes	No	No	No	Dopa, Dobut
4	21	35	100	No	No	Yes	No	Yes	No	Dopa, Dobut
5	21	31	100	Yes	No	No	No	Yes	No	Dopa, Dobut
6	7	32	100	Yes	No	No	Yes	No	No	Dopa, Dobut
7	5	29	100	Yes	No	No	Yes	No	No	Dopa, Dobut
8	5	44	100	Yes	Yes (no response)	No	Yes	No	No	Dopa, Dobut
9	2	44	96	No	Yes (no response)	Yes	Yes	No	No	Dopa, Dobut
10	19	45	100	No	Yes (no response)	No	Yes	Yes	No	Dopa, Dobut
11	4	30	100	Yes	No	Yes	Yes	No	No	Dopa, Dobut
12	4	22	100	Yes	No	Yes	No	No	No	Dopa
13	19	36	100	No	No	Yes	Yes	No	No	Dopa, Dobut

PIP: peak inspiratory pressure

*Dopa: dopamine; Dobut: dobutamine

TABLE III: OUTCOME DATA

S/N	Airleak	Duration of oxygen dependency (days)	Cause of death
1	No	15	
2	Yes	16	
3	No	60	Congenital CMV
4	No	Home oxygen	
5	No	21	Coronary aneurysm
6	No	7	
7	No	6	
8	No	11	
9	No	2	PPHN
10	Yes	Home oxygen	
11	Yes	5	
12	Yes	8	
13	No	25	

CMV: cytomegalovirus; PPHN: persistent pulmonary hypertension

Ventilatory Strategy

There is to date no uniform agreement amongst neonatologists as to the optimum ventilatory approach. Hyperventilation is used widely.⁸ In hyperventilation, high ventilatory pressures and rates are used to induce low PaCO₂ and respiratory alkalosis.² It is thought that the alkalosis will have the desired effect of pulmonary vasodilatation. However, concerns have been expressed regarding the effects of low PaCO₂ and cerebral vasoconstriction as well as neurosensory hearing deficits.⁹

Since June 1994, we have used conservative ventilation as advocated by Wung et al.⁴ In this strategy, high PIPs are avoided. There is no attempt made to achieve low PaCO₂ or alkalosis (even though this is sometimes observed with the high ventilatory rate technique). The

goal is to achieve $\text{PaO}_2 \geq 50 \text{ mmHg}$. There is some evidence that the application of high ventilatory pressures may lead to compression of the pulmonary vasculature which envelop the alveoli. This may adversely affect the pulmonary vascular resistance and thus exacerbate the PPHN. Thus in our treatment strategy, avoidance of high PIP is the key feature of treatment. The target set is $\text{pH} > 7.2$, preductal $\text{PaO}_2 \geq 50 \text{ mmHg}$ and $\text{PaCO}_2 < 60 \text{ mmHg}$.

In conservative ventilation, two ventilatory techniques are utilized. All infants are initiated with low ventilatory rate strategy (rate 20 to 40 per minute, PIP 20 to 30 cmH_2O). High ventilatory rate (100 per minute, PEEP 0) is used if $\text{PaO}_2 \leq 50 \text{ mmHg}$ on optimum low ventilatory rate or PIP > 30 to 35 cmH_2O . In this series all 13 infants had a trial of high ventilatory rate. Nine infants responded. Infants who did not respond to high ventilatory rate were switched back to low ventilatory rate and other rescue therapies (see below) were considered. With high ventilatory rate technique, sometimes low PaCO_2 is seen. This is however, not the objective. The goal is to achieve $\text{PaO}_2 \geq 50 \text{ mmHg}$ at lower PIP.

In severe cases, we aim for preductal $\text{PaO}_2 \geq 45$ to 50 mmHg . A lower postductal PaO_2 may be accepted. This is especially when PIP used is $\geq 35 \text{ cmH}_2\text{O}$. The preductal $\text{SaO}_2/\text{PaO}_2$ reflects the circulation to the brain and the postductal $\text{SaO}_2/\text{PaO}_2$ reflects the circulation reaching the gut, kidneys and lower part of the body. From experience in severe birth asphyxia, these organs (intestines, kidneys) usually recover even after a severe hypoxic insult.¹⁰ The brain, however, may suffer irreversible damage and thus, preductal $\text{SaO}_2/\text{PaO}_2$ should not be compromised. Neurodevelopment outcomes in infants managed by conservative ventilation are encouraging.”

The use of lower ventilatory pressures also reduces the risk of airleak and barotrauma. In addition, venous return will not be so compromised. This is important in maintenance of a satisfactory systemic blood pressure.¹²

Use of Alternative Rescue Therapies

Three forms of rescue therapies are used, especially when the ventilatory pressure requirements are high:

a) Use of a pulmonary vasodilator

Tolazoline and MgSO_4 ,¹³ the 2 vasodilators used in this study, are non-specific for the pulmonary circulation and thus may be complicated by systemic hypotension. Inhaled nitric oxide,¹⁴ which is specific to the pulmonary vasculature, is now considered a superior alternative and we are actively exploring its use in our unit.

In order for the pulmonary vasodilator to have the desired effects, it should be used when PIP is not too high. Too high ventilatory pressure may mechanically compress the pulmonary vessels hence negating any effects of the pulmonary vasodilator. Recent evidence of the failure of action of inhaled nitric oxide with high

ventilatory mean airway pressure (MAP) has been reported.”

We give our intravenous pulmonary vasodilator in the upper limb or scalp veins. This is to take advantage of the pulmonary distribution of the venous return from the upper limbs and scalp veins to the pulmonary artery like in the case of the foetal circulation.

b) High frequency ventilator

Clark et al¹⁶ have reported the use of high frequency oscillatory ventilator in the rescue of infants with severe PPHN. We have only available in our unit an Infant Star[®] ventilator which has been adapted to provide high frequency interruptor ventilation. One of 4 infants actually responded to this modality of treatment.

c) Surfactant

This is considered when a diagnosis of respiratory distress syndrome is made. Also severe MAS may benefit from surfactant therapy.¹⁷ We use Survanta[®].

Use of Paralysing Agents

We do not use paralysis in our strategy for managing PPHN. In the hyperventilation strategy, infants are commonly paralysed. By avoiding paralysis, spontaneous ventilation in the infant is maintained. This spontaneous respiration will contribute to the overall ventilatory needs of the infant and would reduce the mechanical ventilatory requirement, and its associated risks. Also the relative negative intrapleural pressure generated by spontaneous breath (inspiration) will promote systemic venous return to the heart. This will contribute to the maintenance of systemic blood pressure.¹²

Paralysis may further impair the ventilation-perfusion balance by redistributing the pulmonary blood flow to more dependent areas which are less well aerated. In a child who is not paralysed, his/her activity status may give valuable clues to the state of the child as well as alerting one early to the possibility of a partially blocked endotracheal tube.

ECMO has been used in many cases of severe PPHN. However it is not widely available, and it is an expensive as well as an invasive modality of treatment. Concerns remain regarding the long-term outcome of survivors.³ Also with the successes reported with inhaled nitric oxide,¹⁴ it is possible that the need for ECMO may be reduced even further.

In conclusion, we report here our experience in the management of 13 infants with severe PPHN meeting ECMO criteria. Our treatment strategy involves the use of conservative ventilation, no paralysis and use of alternative rescue therapies if high ventilatory pressures are needed. Low mortality due to PPHN can be achieved using this strategy. There is a need to conduct a properly randomised controlled trial to compare this strategy with alternative treatment strategies.

REFERENCES

- Walsh-Sukys M C. Persistent pulmonary hypertension of the newborn. *Clin Perinatol* 1993; 20:127-41.
- Fox W W, Duara S. Persistent pulmonary hypertension in the neonate: Diagnosis and management. *J Pediatr* 1983; 103:505-12.
- Schumacher R E, Palmer T W, Roloff D W, LaClaire R A, Bartlett R H. Follow-up of infants treated with extracorporeal membrane oxygenation for newborn respiratory failure. *Pediatrics* 1991; 87:451-7.
- Wung J T, James L S, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985; 76:488-94.
- Bartlett R H, Roloff D W, Cornell R G, Andrews A F, Dillon P W, Zwischenberger J B. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. *Pediatrics* 1985; 76:479-87.
- Short B L, Miller M K, Anderson K D. Extracorporeal membrane oxygenation in the management of respiratory failure in the newborn. *Clin Perinatol* 1987; 14:737-48.
- Dworetz A R, Moya F R, Sabo B, Gladstone I, Grass I. Survivals of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. *Pediatrics* 1989; 84:1-6.
- Walsh-Sukys M C, Cornell D J, Houston L W, Keszler M, Kanto W P. Treatment of persistent pulmonary hypertension of the newborn without hyperventilation: An assessment of diffusion of innovation. *Pediatrics* 1994; 94:303-6.
- Hendricks-Munoz K D, Walton J P. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 1992; 90:392-6.
- Walfarn F. The post asphyxic syndrome: Clinical management and outcome. In: Pomerance J J, editor. *Neonatology for the Clinician*. Connecticut: Appleton and Lange, 1993:435-51.
- Mason M J, Crisafi M A, Driscoll J M, Wung J T, Driscoll Y T, Fay T H. Hearing and neurodevelopment outcome in survivors of persistent hypertension of the newborn. *Pediatrics* 1992; 90:392-6.
- Adelaidn M M, Michael R P. Hemodynamic effects of mechanical ventilation. *Contemporary management in critical care. Mechanical Ventilation Assisted Respiration* 1991; 1:73-90.
- Tolsa J F, Cotting J, Sekarski W, Payot M, Micheli J L, Calame A. Magnesium sulphate as an alternative and safe treatment for severe persistent pulmonary hypertension of the newborn. *Arch Dis Child* 1995; 72:F184-7.
- Abman S, Kinsella J. Inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics* 1995; 96:1153-5.
- Hoffman G M, Weilin L D. Interaction of mean airway pressure and inhaled nitric oxide on gas exchange. *Pediatr Res* 1997; 41:192A.
- Clark R H, Yoder B A, Sell M A. Prospective randomised comparison of high frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. *J Pediatr* 1994; 124:447-54.
- Findlay R D, Taensh W, Walther F J. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* 1996; 97:48-52.