Persistent pulmonary hypertension of the neonate in a developing country — does extracorporeal membrane oxygenation have a role to play?

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Abstract **A retrospective study was undertaken of survival after conventional management of 35 infants suffering from persistent pulmonary hypertension of the neonate (PPHN). The outcome of infants weighing more than 2 000 g and who also qualified for extracorporeal membrane oxygenation (ECMO) therapy on the grounds of published criteria was assessed.**

The admission incidence of patients with PPHN was 1,1%. Secondary PPHN was more common than primary. The overall survival rate of 69% in this study reflects the trend in recently reported improved survival rates of infants with PPHN, treated with conventional techniques. Sixteen of 28 infants weighing more than 2 000 g qualified for ECMO therapy; 4 of them died. Had ECMO been available as an alternative mode of therapy, only 2 of the 4 might have been saved. The other 2 were considered to have conditions incompatible with a normal quality of life. We therefore assessed the requirement for ECMO in our population to be approximately 0,6/1 000 live births. Although ECMO may be promising, the introduction of this technique in developing countries should rather be delayed until more substantial data refute this. Because PPHN could be related to a potential preventable cause in almost 80% of cases, we propose the support of more cost-effective strategies such as continuing obstetric and perinatal education programmes.

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Persistent pulmonary hypertension of the neonate (PPHN) is a syndrome in which severe hypoxaemia and right-to-left shunting of blood through the foramen ovale and/or ductus arteriosus occur in neonates without recognisable cardiac abnormalities. It is often a complication of acute or chronic perinatal asphyxia, meconium aspiration syndrome, severe hyaline membrane disease, hyperviscosity, lung hypoplasia syndromes, and β-haemolytic streptococcal and other pneumonias.[1-3] It is primarily a disease of full-term and post-term infants and is associated with high morbidity and mortality rates. Despite aggressive management with mechanical hyperventilation, plasma volume expanders and vasopressor drugs, the mortality rate of PPHN reportedly varies between 34% and 60% (average 40%).[1,4-6] Alternative modes of therapy, such as high-frequency oscillatory ventilation and extracorporeal membrane oxygenation (ECMO), have been suggested to improve the outcome of neonates whose respiratory failure is refractory to conventional mechanical ventilation management.[7-9] ECMO entails the use of a modified cardiopulmonary bypass circuit to supply temporary support and lung rest for near-term infants with respiratory failure.

ECMO, however, is costly and labour-intensive, the benefits are controversial, and it has as yet not been used in developing countries. It is also clear from the reported experience of some centres that the survival rate without ECMO is equally good.[10-12]

In this report we describe the incidence, management and short-term outcome of infants with PPHN who were mechanically ventilated, and discuss the possible role of ECMO in a developing country.

Patients and methods

The records of all neonates with PPHN who were admitted to the neonatal intensive care unit (NICU) of Tygerberg Hospital between June 1986 and October 1990 (53 months) were analysed retrospectively.

PPHN was diagnosed if a clinical suspicion of the condition existed based on the presence of severe, labile hypoxaemia disproportionate to the severity of pulmonary disease (confirmed by a positive response to hyperoxia-hyperventilation) and/or echocardiography.[3] Babies with a congenital diaphragmatic hernia or congenital heart lesions were excluded.

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Each baby's chart was reviewed and the severity of respiratory failure assessed for the first 10 hours after initiation of conventional mechanical ventilation. The alveolar-arterial oxygen difference ($AaDO_2$)(kPa), and arterial alveolar oxygen ratio (a/APO_2) were calculated (reflecting the degree of compromise in oxygenation) as well as the oxygenation index (OI) and ventilatory index (VI 1) (reflecting the severity of respiratory compromise and the amount of ventilatory support required, respectively).[13,14] These indices were also calculated to evaluate whether patients who met the criteria for ECMO[3,7,8] would have benefited from that therapy, and to assist in the prediction of outcome, i.e. survival or death. Entry criteria for ECMO were similar to those used in former studies for infants weighing more than 2 000 g, with minor modifications.[3,7,8,10] To qualify for ECMO, infants had to fulfil one or more of the following criteria: (*i*) average arterial alveolar oxygen ratio $\leq 0,1$; and/or (*ii*) mean peak inspiratory pressure (PIP) $\geq$ 30 cm H_2O (mean airway pressure (MAP) $\geq$ 15 cm H_2O) over the first 10 hours of mechanical ventilation; (*iii*) air leaks (pulmonary interstitial emphysema or pneumothorax; and (*iv*) an $AaDO_2$ > 80 kPa for > 4 hours.

Ventilatory and medical management

During the study period the objective of mechanical ventilation in infants with PPHN was to select the ventilator settings necessary to achieve a 'critical' arterial carbon dioxide tension ($PaCO_2$) which would reverse the right-to-left shunt and ensure an acceptable PaO_2 response. Infants were intubated and ventilated with a conventional time-cycled, pressure-limited infant ventilator (Sechrist, model IV 100B, Sechrist, Calif.). The infants were initially ventilated at high rates (85 - 110/min) to try to achieve the 'critical' $PaCO_2$ at the lowest possible inflating pressure. If this approach failed the ventilation rates were decreased and the inflating pressure increased. Throughout, we tried to maintain the positive end-expiratory pressure below 6 cm H_2O. The fractional concentration of inspired oxygen was adjusted according to the preductal O_2 saturation, and was kept between 86% and 94%. In all infants the inspiratory time was $\leq 0,45$ seconds. A continuous infusion of sodium bicarbonate (4,2%) at a rate of 1 mmol/kg/h was administered to infants where a pH $\geq$ 7,42 could not be achieved by ventilation alone. Tolazoline infusion was administered via a peripheral vein in a bolus of 2 mg/kg followed by a continuous infusion of 0,3 - 1 mg/kg/h, when the inflating pressure equalled or exceeded 35 cm H_2O, and the alkaline infusion failed to reverse the pulmonary arterial pressure. The response to this drug was monitored continuously by means of a transcutaneous PaO_2 electrode (Novametrix Medical Systems Inc.) and/or pulse-oximeter (OHMEDA BIOX 3700 pulse oximeter, BOC Health Care). Prophylactic oral antacid therapy was administered to infants receiving tolazoline infusion.

The infants were sedated with intermittent intravenous morphine sulphate (0,1 mg/kg) or bolus doses of fentanyl (2 µg/kg). Only 1 of the patients was paralysed. The mean arterial blood pressure was continuously monitored and kept $\geq$ 40 - 45 mmHg by means of continuous cardio-inotropic support (dopamine, 5 - 20 µg/kg/min) and bolus infusions of either stabilised human serum or fresh-frozen plasma (10 - 20 ml/kg). An attitude of 'minimal' handling was adopted for all the infants. Infants were aggressively weaned from the ventilator as they improved clinically and $PaCO_2$ levels between 7 kPa and 9 kPa accompanied by a pH $\geq$ 7,26 accepted.

Statistics

Means and standard deviations were computed for each of the variables and the differences in numerical data between groups compared using the two-tailed Student's *t*-test. Proportion was compared with the chi-square test; in cases of small numbers, Fisher's exact test was used. Statistical significance was accepted at $P < 0,05$. The values in the tables are expressed as the mean of the mean, unless stated otherwise.

Results

Thirty-five neonates with PPHN were evaluated retrospectively. Their mean gestational age was 36,9 ± 3,5 weeks at birth with a mean birth weight of 2,67 ± 0,88 kg. Diagnosis was confirmed by the presence of hyperoxia-hyperventilation in 43% (15/35), preductal-postductal PaO_2 difference of > 2 kPa in 11% (4/35), and by means of echocardiography in 40% (14/35) of the infants. The associated diagnoses of the study population are shown in Table I. The infants comprised 1,1% of the total admissions to the NICU and represented an incidence in our population of 1:1 600 live births during the study period. Their clinical characteristics are displayed in Tables II and III. Comparison of the clinical, ventilatory and laboratory findings of the survivors v. the non-survivors (Table IV) showed significant differences in the mean PaO_2 ($P = 0,02$), pH ($P = 0,009$) and a/A ratio ($P = 0,03$) over 10 hours, and highest pH achieved ($P = 0,01$), first pH ($P = 0,04$), and first $PaCO_2$ ($P = 0,02$). Surviving infants were mechanically ventilated for 5 ± 3 days and received supplemental oxygen for an additional 6 ± 4 days.

TABLE I.
Characteristics of associated conditions in the infants with PPHN

	No.	%
Meconium aspiration syndrome	12	34,3
Asphyxia (no lung disease)	4	11,4
Hyaline membrane disease/pneumonia	7	20
Septicaemia		
Group B streptococci	3	8,6
Unidentified organism	1	2,9
Pulmonary hypoplasia	1	2,9
Idiopathic pulmonary haemorrhage	1	2,9
Rhesus incompatibility	2	5,5
Transient tachypnoea	3	8,6
Twin-twin transfusion syndrome	1	2,9
Total	35	100

TABLE II.
Clinical characteristics of the 35 infants with PPHN

	Mean ± SD	Range
Gender (M/F)	18:17	
Birth weight (kg)	2,7 ± 0,88	0,89 - 4,64
Gestational age (wks)	36,9 ± 3,5	28 - 42
Apgar (5 min)	6,9 ± 2,5	2 - 10
Air leaks (pneumothorax)	9 (26%)	
No. on drug therapy (%)		
Tolazoline	19 (54%)	
Sodium bicarbonate (weight for volume 4,2%)	18 (51%)	
Combination therapy	13 (37%)	
Inborn/outborn	23:12	
Mortality	11 (31%)	
Caesarean section	15 (43%)	

TABLE III.
Ventilatory characteristics of the 35 infants with PPHN during the first 10 hours after initiation of ventilation (mean ± SD)

		Range
Fio_2	0,93 ± 0,09	0,66 - 1,0
PIP (cm H_2O)	29 ± 7,5	19 - 46
PEEP (cm H_2O)	4,7 ± 1,3	2 - 9
MAP (cm H_2O)	15,8 ± 4,3	7 - 27
Ventilation rate (/min)	78,6 ± 11,6	40 - 100
IPPV (d)	4,8 ± 3,2	1 - 14
PIP (highest value)	35,8 ± 10,1	20 - 60
Ti (s)	0,34 ± 0,03	0,29 - 0,4

Fio_2 = fractional concentration of inspired oxygen; PEEP = positive end expiratory pressure; IPPV = intermittent positive pressure ventilation; Ti = inspiratory time.

TABLE IV.
Profile of survivors v. non-survivors

	Survivors (N = 24)	Non-survivors (N = 11)	
	Mean ± SD		P-value
Birth weight (g)	2 829 ± 790	2 334 ± 1 060	NS
GA (wks)	37,4 ± 3,0	35,7 ± 4,2	NS
Apgar (5 min)	7,4 ± 2,4	5,8 ± 2,7	NS
Pao_2 (kPa) (mean for 10 h)	10 ± 3,5	7 ± 3	0,02
First $Paco_2$ (kPa)	6,2 ± 1,9	8,0 ± 2,8	0,02
$Paco_2$ (mean for 10 h)	5,2 ± 1,0	6 ± 2	NS
Lowest $Paco_2$ (kPa)	3,3 ± 0,8	3,9 ± 1,5	NS
pH (first)	7,20 ± 0,19	7,05 ± 0,18	0,04
pH (mean pH over 10 hours)	7,31 ± 0,1	7,18 ± 0,16	0,009
Highest pH	7,49 ± 0,1	7,36 ± 0,16	0,01
VI 1	2 396 ± 737	2 460 ± 992	NS
$AaDo_2$ (kPa)	72 ± 9,5	74 ± 12	NS
a/APo_2	0,13 ± 0,05	0,09 ± 0,05	0,03
OI	24 ± 14	36 ± 27	NS

GA = gestational age.

Twelve infants were extra-uterine transferrals from peripheral (level II) nurseries. Differences between the inborn and outborn infants were only found for gestational age (P = 0,04) and birth weight (P = 0,02) (Table V). Seventeen infants (48,5%) were of a gestational age above 37 weeks and 14 (82%) of them had either meconium aspiration syndrome (N = 12) or asphyxia neonatorum (N = 2).

TABLE V.
Characteristics of the inborn infants v. outborn infants (mean ± SD)

	Infants		
	Inborn (N = 23)	Outborn (N = 12)	P-value
Birth weight (g)	2 431 ± 918	3 139 ± 675	0,02
GA (wks)	36 ± 3,9	38,5 ± 1,7	0,04
Apgar 5 min	6,5 ± 2,5	7,5 ± 2,7	NS
Survival	15 (65%)	9 (75%)	NS
MAS	6/23	6/12	NS
a/APo_2	0,12 ± 0,05	0,11 ± 0,06	NS

MAS = meconium aspiration syndrome.

Tolazoline was administered to 19 infants (54%) and resulted in improved oxygenation (positive response) in 47% of cases. Air leaks (pneumothorax) developed in 26% of the infants.

The best markers for a very poor outcome were a single a/APO_2 value ≤ 0,05 (N = 3) (100% mortality) or an OI value ≥ 60 (N = 3) (100% mortality). Twenty-eight infants had a birth weight > 2,0 kg and 16 of them were eligible for ECMO on the grounds of fulfilling the entry criteria. Of the abovementioned 16 infants, 4 (25%) died. Their diagnoses included severe lung hypoplasia with renal dysplasia (N = 1), meconium aspiration syndrome (N = 1), β-haemolytic *Streptococcus* (N = 1) and severe refractory asphyxia neonatorum (N = 1). Excluding the last-mentioned infant (who also had multi-organ failure and was assessed as having a condition incompatible with a normal quality of life) only 2 infants of this group of infants who succumbed, might ultimately have been saved by means of ECMO (i.e. the 1 infant with meconium aspiration syndrome and the 1 with β-haemolytic *Streptococcus* infection), had it been available.

Discussion

PPHN secondary to meconium aspiration syndrome and asphyxia is still relatively common in developing countries such as South Africa. This is partly due to factors such as no or poor antenatal attendance at clinics, socio-economic factors, logistic problems such as transport, and incorrect assessment and resuscitation of distressed infants by attending physicians and/or nursing staff. Until these conditions can be prevented or rectified, it is important for paediatricians to be familiar with the diagnosis and treatment of PPHN. To improve survival rates, these infants must be managed where specific technology and experience exist. In South Africa these facilities are mostly limited to the tertiary institutions, as well as some large provincial and private hospitals.

At Tygerberg Hospital the treatment of infants with PPHN focuses on mechanical ventilation, as other alternatives such as ECMO and high-frequency oscillatory ventilation are either too expensive or unobtainable. With this approach the survival rate of 69% in the present study compares well with those from similar studies reported by Hageman *et al.*[6] (71%) and Bifano and Pfannenstiel[15] (72%). Potential problems related to aggressive mechanical ventilation include acute and chronic lung injury and the effects of hypocarbia on cerebral blood flow.[15-17] The incidence of pneumothorax in this study (26%) is lower than that reported by Fox[18] (> 50%), Hageman *et al.*[6] (35%), Wung *et al.*[10] (40%) and Kohelet *et al.*[7] (46%). The incidence of bronchopulmonary dysplasia among the survivors in the present study was 3% while 1 infant developed a wheezy chest after the neonatal period. The abovementioned low frequency of lung sequelae reflects our unit's conservative approach to positive pressure ventilation, where higher $Paco_2$ values (5,4 ± 1,2 kPa) are regarded as acceptable during the acute stages of PPHN, and infants are aggressively weaned during the transitional phase of their disease. To achieve this, transcutaneous Pao_2 and $Paco_2$ monitors are continuously utilised.

This study also showed that non-survivors spent significantly more time poorly oxygenated (P = 0,02) and acidotic (P = 0,009) compared with the survivors. This is probably a reflection of more severe PPHN in the non-survivors with increased right-to-left shunting (a/APo_2 ratio difference significant, P = 0,03).

The development of PPHN in the present study could be related to a potentially preventable predisposing factor in 80% of the enrolled infants. Meconium aspiration syndrome was the primary diagnosis in 12 infants (34%) and remains one of the principal, preventable causative factors in PPHN. Of great concern is the nearly doubled incidence of meconium aspiration syndrome among outborn infants (50% v. the 26% incidence (P = NS) in the inborn infants). Since the introduction of ECMO by Bartlett *et al.*[9] in 1976, more than

3 000 term or near-term infants have been treated with this form of therapy, resulting in a survival rate of almost 83%. ECMO, however, is not benign or inexpensive, as the morbidity and incidence of permanent neurological injury in patients who undergo ECMO are substantial. Approximately 10 - 15% of neonates may die and 10 - 30% of surviving infants have an adverse neurodevelopmental outcome.[17,19] The technique of ECMO is labour-intensive and requires the constant attention of an experienced physician assisted by trained technologists and nursing staff.

In conclusion, our data reveal a PPHN incidence of 1,1% of admissions to the NICU, with meconium aspiration syndrome (34%) the leading causative factor. The survival rate of 69% achieved in the present study with conventional techniques reflects the trend of improved survival reported recently.[20] Had ECMO been available as an alternative mode of therapy at Tygerberg Hospital, only 2 additional infants might have been saved (requirement for ECMO: ± 0,6/1 000 live births). It seems that ECMO has little to offer to improve survival of infants with PPHN in our situation, and that in a developing country such as South Africa, it would be of more value to focus on the improvement of obstetric and perinatal education programmes.[21]

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