

## Persistent Pulmonary Hypertension of a Newborn

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### Abstract

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a pathological condition that results from an abnormal transition of the pulmonary circulation at birth. It is marked by an increase in pulmonary vascular resistance leading to significant morbidity and mortality in newborns, hence the need for an early etiological diagnosis with adequate management.

We present the case of a newborn who presented neonatal respiratory distress at birth, and whose evolution was complicated by the onset of a pneumothorax. The paraclinical evaluation of the newborn revealed pulmonary hypertension confirmed by echocardiography, which showed a dilatation of the pulmonary artery with dilatation of the right cardiac cavities, a patent ductus arteriosus (PDA) and a patent foramen oval (PFO). The management of the patient was centred on effective ventilation with adapted oxygen therapy, resulting in clinical improvement with progressive regression of the respiratory distress and subsequent resolution of the secondary pulmonary hypertension.

In view of the newborn's difficulties in adapting to extra-uterine life, and the resulting complications, it is crucial to be aware of the pathophysiology of PPHN as well as the different therapeutic means proposed, in order to alleviate the short and long term complications of this pathology.

**Keywords:** Pulmonary Hypertension; Newborn; Respiratory Distress; Etiology; Treatment

### Introduction

Persistent pulmonary hypertension (PPHN) is a consequence of failed pulmonary vascular transition at birth characterized by sustained elevation of pulmonary vascular resistance, leading to right to left shunting of blood through foramen oval (FO) and ductus arteriosus (DA) and preventing the increase in pulmonary blood flow. It is often associated with certain diseases such as birth asphyxia or respiratory distress, causing multiple complications including neurological injury, multiorgan dysfunction and death [1,2].

### Case Report

We present a case of a male non-consanguineous patient, born to a mother aged 21 years old, with two parity and gestations, and two living children by caesarean section, with no particular medical history, whose pregnancy was well attended, estimated at 35 weeks +6 days according to date of last menstrual period, and at 39.1 weeks according to the FAAR score, the birth took place by caesarean section for acute foetal distress due to decelerations that were objectively related to the recording of the foetal heart rate, the Apgar at birth was

10/10 at the 1<sup>st</sup>, 5<sup>th</sup> and 10<sup>th</sup> minute, the cry was immediate, the amniotic fluid was clear, and the infectious anamnesis was positive regarding a neonatal respiratory distress set up before the 4<sup>th</sup> hour of life. The latter was rated at 5/10 according to Silvermann's scale with the presence of a minimal nasal flaring, an intercostal retraction and an audible grunt. The patient was subsequently placed on non-invasive ventilation (CPAP CNO type) as well as combined 3<sup>rd</sup> generation cephalosporin and gentamycin antibiotic therapy. The biological (Cell blood count, C-reactive protein, ionogram and blood culture) and radiological (chest X-ray) results were without any particularities aside from a positive blood culture with a coagulase negative staphylococcus. On his second day of life the patient worsened his respiratory symptoms, a control chest X-ray revealed the onset of a minimal pneumothorax in the right lung field with a right basithoracic alveolar syndrome, suggesting pulmonary hypertension confirmed by echocardiography, which revealed a dilatation of the pulmonary artery to 8.1 mm compared to the aorta with a diameter of 7.7 mm, it also objectified a dilatation of the right cardiac chambers, with a minimal PDA and PFO.

In view of the pneumothorax, we had put the patient under oxygen goggles at a flow rate of 1L, thus avoiding additional barotrauma. A 3<sup>rd</sup> control chest X-ray was requested which marked a spontaneous resolution of the pneumothorax. The newborn was then put back on CPAP CNO with a flow rate of 8, a fraction of inspired oxygen (FiO<sub>2</sub>) of 40% and an aid of 2. By progressively decreasing the parameters of this ventilation (FiO<sub>2</sub> and aid), the patient was weaned after 4 days. The evolution was marked by a clinical and radiological improvement with a control echocardiography that objectively showed the disappearance of pulmonary hypertension.

### Discussion

During fetal life gas exchange take place at the placenta, with a reduced pulmonary blood flow (PBF) because of the elevated pulmonary vascular resistance (PVR), therefore, most of the right ventricular output crosses the DA to the aorta [3]. At birth a progressive transition from fetal to extrauterine life is expected to occur, by a succession of cardiopulmonary adaptations. Clamping of the umbilical cord removes the placental low resistance circulation and increases systemic vascular resistance (SVR), resulting with a rapid increase in arterial pressure and reduction in cardiac output [4]. Simultaneously, the PVR decreases rapidly with an increase in PBF 8 to 10 fold, which results in an increase in right atrial pressure and closure of the FO. Consequently PVR is lower than the SVR, the flow reverses across the PDA, the increase in arterial oxygen saturation also leads to closure of the DA and ductus venosus [1,3,4].

The PVR declines as well as a result of the first postnatal breath, with lung distension and the onset of ventilation, resulting in an increase in alveolar oxygen tension. Those physical stimulation leads to pulmonary vasodilation by increasing production of vasodilators, such as NO and prostacyclin (PGI<sub>2</sub>) [1,3].

The pathogenesis of PPHN is multifactorial, it include sustained elevation of PVR and hypoxemia secondary to right to left extrapulmonary blood flow shunting across DA or FO. Two essential mechanisms may be involved, an increased pulmonary arteriolar vasoconstriction and vascular structural remodeling, with or without underdevelopment of pulmonary vascular bed, involving several perinatal risk factors [1,2].

The one that are significantly associated with a higher risk for PPHN are either antennal such as low maternal education, black or Asian race, high prepregnancy BMI, diabetes, gestational hypertension and preeclampsia, male infants, the presence of asthma in the mother, maternal smoking, and the use of inhaled steroids or b-agonists, or perinatal risk factors such as late preterm newborn, and macrosomia [5,6]. Hernandez-Diaz, *et al.* suggests that infants delivered by cesarean section are at a higher risk to develop a PPHN, in a control group of 61 nonmalformed newborns, 49.2% had elective cesarean sections and 18% had emergency cesarean sections because of either fetal distress or other factors, among those with cesarean section, fetal distress was identified in 38.5% of the case [5], as it has been objectified in our patient.

As previously mentioned the etiologies of PPHN are broadly related to pulmonary vasoconstriction seen in sepsis, perinatal asphyxia, meconium aspiration syndrome, or respiratory distress syndrome, and to vascular remodeling observed in cases of idiopathic PPHN such

as newborns exposed to chronic intrauterine hypoxia seen in premature closure of DA. Hypoplastic vasculature is also an etiology of PPHN related to congenital diaphragmatic hernia (CDH) and other causes of pulmonary hypoplasia (oligohydramnios secondary to Potter's Syndrome, renal disease or chronic leakage of amniotic fluid), additionally polycythemia result in intravascular obstruction leading to an elevated PVR [1,5-8].

Treatment of PPHN depends on the underlying etiology, aiming to decrease PVR and reducing the right to left shunt, through pulmonary vasodilators. Inhaled nitric oxide (iNO) is the only approved pulmonary vasodilator specifically for the treatment of PPHN, it is the most studied and accepted treatment, he has been proven safe for neonates, without systemic adverse events or long-term use toxicity [1], it recommended at a dose of 10 - 80 ppm initiated if  $\text{PaO}_2 < 100 \text{ mmHg}$  with 100%  $\text{O}_2$  [9], however many patients remains NO resistant hence the need of additional therapies. PDE5 inhibitors mainly sildenafil, are currently studied, available trials are limited. It is used as adjuvant in iNO resistant PPHN or as monotherapy when iNO is not available or contraindicated, as well as in associated PH to CDH and bronchopulmonary dysplasia [10] it is given at a dose of 0.5 - 3.0 mg/kg every 6h (IV, oral or inhaled) [11], Tadalafil is another PDE5 inhibitor approved for adult but no studies in newborns have been performed [1]. In addition, L-Citrulline ameliorate PPHN by improving NO production yet no trials regarding its use in newborns have been performed [1]. Prostaglandin (PG) analogs can be complementary to iNO, with two studied classes PGI2 (iloprost, Treprostinil and beraprost) [1] and PGE1 (alprostadil) [12], they potentially improve oxygenation in iNO resistant infants [1], PGE1 have a pulmonary vasodilator effects, it is also set to maintain patency of DA which may offer an advantage for neonates by reducing right ventricular pressure overload [12], yet small studies have been suggesting PGI2 analogs as valuable treatment for PPHN [13,14]. PDE3 inhibitors (milrinone) is an effective therapeutic option in infants with PPHN, particularly if iNO resistant (as in CDH) or in cardiac dysfunction, considering its effects (inotropic and lusitropic) [1], it may used in a dose 0.33 - 0.99 mcg/kg/min [15]. Bosentan is a non-selective endothelin-1 receptor antagonist, evidence of its efficacy and safety is limited, it may be of particular interest in the chronic management of infants with iNO-resistant PH, Maneenil G., *et al.* suggest an oral dose of 1 mg/kg, [1,16]. Our patient went through a mechanical ventilation with oxygen therapies, both extremes of oxygen content in the neonatal lung should be avoided in PPHN, hypoxia is a pathogenic factor in PPHN, however hyperoxia has also been extensively studied and might be just as harmful as hypoxia for the onset and perpetuation of pulmonary vascular dysfunction [1], however an optimal lung expansion is essential for adequate oxygenation, ventilation strategies are recommended to ensure this expansion. Avoiding barotraumas is essential as well [2], Wung., *et al.* suggest that  $\text{PaO}_2$  should be in the range of 50 to 70 mmHg and  $\text{PaCO}_2$  between 40 and 60 mmHg [17], still some infant may become agitated with the ventilator, increasing catecholamine release, and resulting in increased PVR, application of sedatives is a common either by benzodiazepine or narcotic agents [2]. Other therapies might be effective for the management of PPHN such as surfactant therapy and glucocorticoids that has been shown to improve oxygenation [2], furthermore the clinician needs to be alert to the possibility of nosocomial infection that can contribute to infants' mortality [1]. Although infants who fail to respond to medical management require treatment with extracorporeal membrane oxygenation (ECMO) [2] as an ultimate therapy.

Nevertheless, PPHN is a life-threatening condition, it can, in most cases, be reversible within the first days of life, alongside with the improvement of the associated etiology [1] as seen in our case. The outcomes of infants with PPHN are mainly determined by their underlying diseases, feeding problems and short-term respiratory morbidities can be seen, high risk of neurodevelopmental disabilities including hearing loss, cerebral palsy and delays in either cognitive or motor performance [2,18].

### Conclusion

Persistent pulmonary hypertension is a frequent event affecting infants in the neonatal intensive care unit, management strategies have improved, however the morbidity and mortality associated with this condition remains high. Thus, the need to understand the mechanisms underlying PPHN as well as the development of additional pharmacotherapies.

### Conflicts of Interest

The authors declare no conflict of interest.

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