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Pulmonary Hypertension in the Newborn: More Than Persistent Hypoxemia: Case Report and Literature Review

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Abstract: ***Persistent pulmonary hypertension of the newborn is a clinical condition with a low global incidence (2 to 4 per 1000 live births), predominant in premature and post-term infants, yet with significant mortality (up to 33%). The comprehensive management of this syndrome, characterized by persistent and severe hypoxemia due to failure in fetal circulation transitioning to extrauterine life, poses a real challenge in low and middle-income countries. This is primarily due to limited availability and high costs of first-line therapies such as nitric oxide once the diagnosis is established. We present a case from a referral institution in Barranquilla, Colombia, of a 32-week male newborn with early neonatal sepsis, hyaline membrane disease, and marked clinical deterioration, diagnosed with pulmonary hypertension by echocardiography. He was managed with nitric oxide and simultaneous high-frequency mechanical ventilation for 24 hours, showing an adequate response. Additionally, a phosphodiesterase type 5 inhibitor and inodilator were adjunctively administered, resulting in subsequent reduction and normalization of pulmonary pressure.***

Keywords: Pulmonary hypertension, fetal circulation, newborn, nitric oxide, mechanical ventilation

1. Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is defined as sustained elevated pulmonary vascular resistance (PVR) with normal systemic vascular resistance (SVR) due to disruptions in postnatal circulatory transition, leading to restricted pulmonary circulation characterized by severe acute respiratory failure and consequent hypoxemia (1). It remains a significant cause of morbidity and mortality in neonates despite improvements in management. The incidence is estimated at approximately 2 cases per 1000 births. Etiology may stem from pulmonary causes or cardiac abnormalities. Treatment primarily revolves around the use of nitric oxide (NO) and pulmonary vasodilator therapy (2).

2. Methodology

The following review consists of a clinical case report and literature review. It involved verifying the patient's medical history, diagnostic tests, medical management, and clinical evolution during their stay in the neonatal intensive care unit, as well as exploring current literature on the pathology to provide an update on novel and successful management approaches.

3. Case Description

This concerns a male preterm newborn at 32 weeks gestation, born from an uncontrolled pregnancy with maternal history of urinary tract infection in the last trimester. There was an urgent cesarean section due to fetal distress (fetal bradycardia) (Apgar scores: 7/10 and 8/10). The patient's weight, height, and head circumference were appropriate for gestational age. During the adaptation period, after 10 minutes presents marked respiratory difficulty (Silverman 5/10), reason for admission to the neonatal intensive care unit (NICU) at the Adelita de Char MIRED IPS university medical care center. Upon admission, a diagnosis of hyaline membrane disease was established, and he received exogenous pulmonary surfactant (Curosurf) at an initial dose of 2.5 mg/kg via the Insure technique. Management continued with nasal non-invasive mechanical ventilation (NIMV) and first-line antibiotic coverage due to maternal risk of early neonatal sepsis.

During his first day in the NICU, he developed hypocalcemia and hemodynamic deterioration characterized by bradycardia, necessitating inotropic support with dopamine at a dose of 10 mcg/kg/min. He responded well clinically; however, there was deterioration in ventilatory mechanics. At 48 hours, he exhibited thoracoabdominal dissociation, requiring increased

ventilatory parameters and posing a risk of ventilatory failure. Consequently, invasive mechanical ventilation was initiated under radiographic guidance, revealing surfactant depletion necessitating an additional dose of exogenous surfactant at 1.25 mg/kg.

During the patient's course of treatment, while requiring high ventilatory parameters, an echocardiogram was performed revealing a pulmonary pressure of 70 mmHg, confirming the diagnosis of persistent pulmonary hypertension of the newborn. The patient required inotropic support with Noradrenaline (0.2 mcg/kg/min), Milrinone (0.2 mcg/kg/min), and pulmonary vasodilators Sildenafil (2 mg/kg/dose). He remained on conventional invasive mechanical ventilation with maximal ventilator settings, decoupled from the ventilator, elevated mean airway pressure, and arterial gases showing mild to moderate hypoxemia, with a P/F ratio of 202, oxygenation index (OI) of 18, respiratory acidemia meeting criteria for high-frequency oscillatory ventilation, and nitric oxide at 20 ppm. After 24 hours of treatment with high-frequency oscillatory ventilation + nitric oxide, a decrease in pulmonary pressure to 52 mmHg was observed, leading to discontinuation of the inodilator (milrinone) and initiation of gradual reduction in FiO2 and nitric oxide. The patient responded well to weaning, showing a significant decrease in pulmonary pressure to 25 mmHg within the next 12 hours. Consequently, the decision was made to discontinue nitric oxide therapy and maintain strict clinical monitoring.

4. Discussion

Persistent pulmonary hypertension of the newborn (PPHN) comprises signs and symptoms characterized by sustained elevation of pulmonary vascular resistances following birth. This condition arises due to disruptions in the transition of neonatal circulation to extrauterine life, resulting in a right-to-left shunt of deoxygenated blood (3).

The reported global incidence of PPHN ranges from 1.8 to 5.4 per 1000 live births, with higher rates observed in late preterm infants compared to term newborns, respectively. A population-based study conducted in California, which included 7,847 infants with PPHN, reported an incidence of 0.2% and an overall mortality of 7.3%. However, a retrospective multicenter Asian study showed a higher incidence ranging from 1.2 to 4.6 cases per 1000 live births (4).

Worldwide, mortality rates in infants with PPHN range from 7% to 15%, which are correlated with the severity of the clinical presentation and the underlying etiology. For instance, organ failure associated with sepsis is linked to early mortality, while congenital anatomical abnormalities contribute to a higher burden of persistent morbidity (5).

Persistent pulmonary hypertension of the newborn (PPHN) can be primary or secondary. The primary form, also known as idiopathic, accounts for approximately 10% of cases, referring to those without parenchymal lung pathology. The secondary form occurs in association with other conditions such as respiratory distress syndrome, meconium aspiration syndrome, transient tachypnea of the newborn, pneumonia, congenital diaphragmatic hernia, pulmonary hypoplasia, or dysplasia (6).

Genetic bases and mutations have been described to play a crucial role, for instance, the gene encoding bone morphogenetic protein receptor 2 (BMPR2), CAV1, KCNK3, and EIF2AK4(6). Nevertheless, deletions have been found in 17q23.2 with an overlapping region harboring the TBX4 gene, including 18 different heterozygous variants, corresponding to patients with idiopathic PPHN who do not respond to conventional management (6).

The gene encoding corticotropin-releasing hormone receptor 1 (CRHR1) and the CRH-binding protein have been associated with this condition, affecting the hypothalamic-pituitary-adrenal axis. Single nucleotide polymorphisms (SNPs) of the CRHR1 receptor are located near the transcription factor binding site for peroxisome proliferator-activated receptor gamma (PPAR-γ), which influences smooth muscle cells in the pulmonary artery and vascular tone (6).

The primary risk factor is prematurity, owing to the various stages of lung development. Depending on the quantity and quality of pulmonary vessels and their resistances, the incidence can vary. For instance, during the canalicular stage (few pulmonary vessels), there is high pulmonary vascular resistance and a small pulmonary bed area. However, at this gestational stage, the pulmonary vasculature is less sensitive to hypoxemia. The incidence increases significantly in weeks 23-26 of gestation, leading to up to a 10-fold increase in the use of inhaled nitric oxide (iNO) once detected. Conversely, in the early saccular phase, rapid proliferation increases the pulmonary bed area, and pulmonary vessels become more sensitive to hypoxemia or other vasoconstrictive mediators like endothelin-1 (ET-1), resulting in lower pulmonary vascular resistance. A later premature birth generally carries a better prognosis in this regard (6).

Several factors contribute to maintaining high pulmonary vascular resistance (PVR) in the fetus. Mechanical conditions such as fluid-filled lungs, exposure to hypoxia, vasoactive mediators, and serotonin are known contributors. In fact, exposure to these factors during the second trimester of pregnancy has been associated with PPHN (6).

The development of pulmonary vasculature can also be influenced by toxic, placental, maternal, or environmental factors. Studies have examined maternal factors such as race (Black or Asian), maternal smoking, NSAID use (particularly late in pregnancy), obesity, asthma, and diabetes. Neonatal factors include male sex, delivery by cesarean section, preterm or post-term birth (<37 weeks - >41 weeks), and fetal macrosomia (7).

Patients with Down syndrome (trisomy 21) often develop this condition along with congenital heart defects and have a 10-fold increased risk of idiopathic PPHN and requiring ECMO (7).

Animal studies have shown that prenatal or postnatal use of corticosteroids normalizes the function of nitric oxide synthase enzyme, thereby improving pulmonary vascular function in PPHN (7).

PPHN results from disruptions or failures in transitional fetal circulation, characterized by persistent elevation of pulmonary vascular resistances and consequently a right-to-left shunt through fetal bypass pathways, such as the ductus arteriosus or patent foramen oval (7).

Physiologically, these patterns, if they persist in extrauterine life, can lead to hypoxemia and respiratory failure. Upon umbilical cord clamping, the low resistance of the uterine artery, combined with the baby's crying, should reverse the resistances, allowing systemic circulation to dominate over pulmonary circulation, facilitating gas exchange. Interruptions in various signaling pathways play a significant role in the described abnormalities in the pathogenesis of PPHN, helping to understand the mechanism of action of the drugs used (7).

The following pathways are identified:

- **Nitric oxide pathway:**

Nitric oxide (NO) is a potent vasodilator released endothelially once endothelial nitric oxide synthase (eNOS) is activated from L-arginine. It acts as a vasoactive mediator stimulated by increased oxygen tension, such as following oxidative phosphorylation with elevated adenosine triphosphate (ATP) levels, increasing pulmonary blood flow and achieving pulmonary vasodilation at birth. This is achieved through diffusion of eNOS to pulmonary arterial smooth muscle cells (PASMC), triggering guanylate cyclase (soluble enzyme) stimulation and producing cyclic guanosine monophosphate (cGMP) as a second messenger, derived from guanosine triphosphate (GTP). Thus, inhibition or interruption of eNOS production or its substrate (L-arginine) reduces metabolites and influences PPHN (6).

Conversely, cGMP is degraded by phosphodiesterase-5, halting smooth muscle relaxation.

- **Endothelin pathway:**

Endothelin-1, produced by vascular endothelium, is a vasoconstrictor of pulmonary arterial smooth muscle cells (PASMC). Its action occurs via ETB and ETA receptors, mediating vasodilation (through the NO-cGMP pathway) and vasoconstriction, respectively. The latter is considered pivotal in the pathophysiology of PPHN, as the ET-1 gene and its elevated concentrations influence vasoconstriction. Conversely, blocking the ETA receptor at the fetal level induces pulmonary vasodilation (6).

- **Rho kinase pathway:**

The enzyme Rho kinase stimulates myosin chain phosphorylation via a guanosine triphosphate (GTP)-binding protein (RhoA), affecting vascular tone and resulting in high pulmonary vascular resistance. The RhoA-Rho kinase pathway mediates hypoxemic vasoconstriction by sensitizing contractile proteins to calcium, which regulates smooth muscle contraction in PASMC cytosolic levels (8).

- **Arachidonic acid pathway:**

This pathway synthesizes prostacyclin (PGI2) through enzymes prostacyclin synthase and cyclooxygenase, utilizing arachidonic acid as a substrate. Within vascular smooth muscle, the PGI2 receptor activates adenylate cyclase upon binding, increasing cyclic AMP (cAMP) generation from ATP. Thus, pulmonary vasodilation is mediated upon ventilation and inflation; however, it is degraded by phosphodiesterase 3A.

It is known that the combination of high levels of nitric oxide and FiO2 can increase phosphodiesterase 3A activity (6).

- **Oxidative stress:**

The vasodilatory properties of oxygen are crucial and undeniable in PPHN, as they reduce pulmonary vascular resistance. Conversely, acidosis increases vasoconstriction in this condition, and PASMCs are sensitive to vasoconstrictive changes induced by reactive oxygen and nitrogen species. Studies have shown that exposure to 100% oxygen can increase superoxide anion production and diminish the response to nitric oxide (6).

Regarding diagnosis, echocardiography is not only the gold standard but also a significant aid in characterizing and treating neonates with PPHN. Echocardiographic evaluation helps rule out structural heart diseases, including those that mimic PPHN. It also determines the predominant direction of shunting, whether through the patent ductus arteriosus (PDA) or patent foramen ovale (PFO). Diagnosis of this condition should not be made without evidence of a bidirectional shunt, typically occurring from right to left via the PDA or PFO. Among the most suggestive echocardiographic signs of pulmonary hypertension are increased systolic time intervals of the right ventricle and flattening of the septum (9).

In newborns with PPHN, traditional echocardiographic assessments of the right ventricle (RV) focus on the direction of the tricuspid regurgitation jet. While this evaluation may be elevated in newborns with PPHN, its absence should not reliably correlate with clinical outcomes, and it may not be optimally measurable in some patients (9).

Management of PPHN should be comprehensive, including addressing metabolic disorders such as hypoglycemia, anemia, hypothermia, and hypovolemia, as well as assessing for sepsis and correcting acid-base disturbances. Close monitoring of vital signs, particularly blood pressure and pulse oximetry (pre- and post-ductal), is essential (9).

If invasive mechanical ventilation is initiated, parameters should be managed according to strategies such as gentle or protective ventilation, advocating for the use of low tidal volumes (9).

Using high-frequency oscillatory ventilation (HFOV) in patients with persistent pulmonary hypertension of the newborn

has short-term beneficial effects, such as improving arterial oxygenation and reducing the need for ECMO. However, the relative efficacy has not been well studied. It is essential to understand that the premise of using HFOV in these patients is based on the failure of conventional ventilation beforehand (12).

The decision to use HFOV is made when reaching maximum parameters, including PEEP between 6-8 cmH2O, PIP of 20-25 cmH2O, frequency of 60 rpm, inspiratory time between 0.25-0.35 seconds, and high FiO2. If these parameters fail to achieve oxygen saturations above 90%, PaO2 above 45 mmHg, and oxygenation indices below 20, the failure of conventional invasive mechanical ventilation is determined, and consideration should be given to initiating HFOV (12).

Nitric oxide (NO) continues to be the only approved pulmonary vasodilator therapy by the Food and Drug Administration in the United States for premature and term newborns with PPHN. It is important to highlight that the selective pulmonary vasodilatory effect occurs because NO is inactivated in the presence of hemoglobin in circulation, thus minimizing systemic vasodilation. The patient's response to NO is not only therapeutic but also diagnostic. Lack of response to the medication is often associated with inadequate pulmonary recruitment (9).

Regarding the use of prostacyclins, cases have been described in the literature where newborns with pulmonary hypertension benefited from inhaled iloprost. These cases involved a term infant with diaphragmatic hernia and a preterm infant with respiratory distress syndrome, respectively (15).

Milrinone is a phosphodiesterase 3 (PDE3) inhibitor that acts by reducing the breakdown of cyclic adenosine monophosphate (cAMP) to its inactive form AMP through the enzyme PDE3. As a secondary effect, this leads to decreased intracellular calcium, resulting in relaxation of vascular smooth muscle cells in the lungs (3).

Sildenafil inhibits phosphodiesterase type 5 (PDE-5), causing pulmonary vasodilation. Studies mentioning its use do so in resource-limited settings where NO is not available, often as adjunctive therapy to NO. These studies reported improvements in oxygenation index and pulmonary arterial pressure; however, there is a lack of robust studies demonstrating safety and efficacy in this population (10).

Due to the quantity and quality of existing studies, it is not possible to determine the equivalence or superiority of Milrinone, Sildenafil, or even a synergistic effect of both, compared to nitric oxide. In fact, the applicability of these studies to high-income countries where nitric oxide is the therapy of choice is unclear (3). However, it has been recommended that in cases of suboptimal response to nitric oxide, sildenafil and milrinone can be added as second or third-line therapies (3).

Tadalafil is a long-acting inhibitor of phosphodiesterase type 5 and is administered once daily. Because this agent is newer compared to Sildenafil, there is less data available in infants, but it appears to be well tolerated and equally effective (11).

Regarding severe refractory respiratory failure, which is the clinical manifestation of severe hypoxemia characteristic of this condition, in the last two decades, the use of high-frequency oscillatory ventilation (HFOV) has been proposed as a rescue therapy. A recent systematic review by Cochrane (2016) considered it a promising treatment for acute respiratory distress syndrome and lung injury (13).

However, despite the limitations of this therapy in preterm infants with severe respiratory failure, in 2021, Hsu JF and colleagues conducted a cohort study to investigate the impacts of dynamic changes in HFOV and other organ failures on mortality, as well as other complementary therapies and independent risk factors for hospital mortality in Taiwan (2011-2018). This study included premature infants unresponsive to conventional mechanical ventilation with severe oxygenation disorder, concluding that HFOV is the most common and widely applicable intervention under these criteria, despite high mortality rates. It was noted that these studied patients, as well as in the present report, concurrently required the use of nitric oxide and cardiac inotropic support, achieving adequate clinical response (14).

5. Conclusion

Persistent pulmonary hypertension of the newborn requires multidisciplinary teamwork involving various specialties. Understanding the risk factors, indications for respective interventions—both general and pharmacological—and determining their suitability in each case not only influences the patient's positive response but also impacts morbidity, mortality, healthcare systems, and access to frontline therapies, even in low to middle-income countries.

6. Future Directions

There are medications for pulmonary hypertension in adults with limited exposure in neonates, including Selexipag, Sotatercept, and Riociguat. Conducting extensive studies of these new pharmacological therapies in newborns is crucial to consider new interventions that impact the effectiveness and safety of using these drugs in our pediatric population.

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