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Pulmonary Hypertension in the Newborn, Pathophysiology, Diagnosis, and Treatment

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Abstract: **Persistent pulmonary hypertension of the newborn (PPHN) is severe cardiopulmonary condition identified by raised mean pulmonary artery pressure (mPAP) and prolonged direct exposure of the right ventricle to high afterload. but more substantial cause of respiratory distress in babies than others like transient tachypnea of newborn, breathing distress syndrome and etc. An incidence is of 1.9 per 1000 live-births (0.4 - 6.8/ 1000 live births) have been reported, and death rate varying from 4 - 33%have been reported. Current study was aim to focus on pulmonary hypertension and mostly on Persistent pulmonary hypertension of the newborn (PPHN). In addition to evaluate the diagnostic procedures, and treatment intervention, and before all that we intended to discuss the pathophysiology of PPHN. Electronic search was conducted through famous medical databases; PubMed/Midline, and Embase, searching literature on Persistent pulmonary hypertension of the newborn (PPHN), we searched studies that were published in English language only, and up to December,2016 and with only human subjects. Moreover, we searched the references lists of each identified article for more relevant studies. PPHN is a prevalent neonatal issue whose trademark medical function is oxygenation failure, yet it represents a spectrum of physiologic factors that need to be considered when making medical choices. Neonatal intensivists must recognize and follow the basic therapeutic method consisting of the judicious use of oxygen, the administration of Inhaled nitric oxide (iNO) and accomplishment of suitable lung recruitment. It is equally essential not to forget the fundamental physiologic reasoning, which forms the basis of this method and is based on management of elevated PVR. When thinking about alternative pulmonary vasodilators or drugs to support best ventricular performance, the latter is most pertinent.**

Keywords: **Persistent pulmonary hypertension of the newborn (PPHN), Diagnosis, and Treatment.**

1. INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is severe cardiopulmonary condition identified by raised mean pulmonary artery pressure (mPAP) and prolonged direct exposure of the right ventricle to high afterload. Physiologically, mPAP is straight related to lung blood circulation (PBF), pulmonary vascular resistance (PVR) and lung capillary wedge pressure (PCWP) and is associated with substantial neonatal morbidity and death [(1)]. Relentless pulmonary hypertension is less typical, but more substantial cause of respiratory distress in babies than others like transient tachypnea of newborn, breathing distress syndrome and etc. An incidence is of 1.9 per 1000 live-births (0.4 - 6.8/ 1000 live births) have been reported, and death rate varying from 4 - 33%have been reported [(2,3)].

The large majority of cases of PPHN are secondary to high PVR. In neonates, PHT is usually secondary to dysregulation of PVR. PHT is a frequent diagnosis in tertiary neonatal intensive care units and might develop secondary to a large range of diseases. Broadly, PHT in neonates can be described as chronic or acute (**Figure 1**) [(3)], which are identified by intrinsic differences in their pathophysiology and medical discussion [(4)]. While severe episodes of neonatal PHT might occur later on in neonatal diseases (e.g., secondary to sepsis), the most typical discussion remains in the immediate postnatal duration, secondary to irregular shift of the pulmonary flow from a high-resistance intrauterine to a low-resistance extrauterine circuit. This particular discussion of severe lung hypertensive crises is extensively described as persistent

pulmonary high blood pressure of the newborn (PPHN). Chronic PHT, on the other hand, happens due to secondary rise in PVR following preliminary effective postnatal transition, and is seen most regularly as a secondary problem of chronic neonatal lung disease in too soon born neonates [5,6].

In some newborns, the normal decline in pulmonary vascular tone does not happen and ultimately leads to PPHN. With inadequate lung perfusion, neonates are at risk for establishing refractory hypoxemia, breathing distress, and acidosis [7]. PPHN is usually acknowledged in term or near-term neonates, however it can occur, albeit infrequently, in premature neonates. Regardless of the intro of treatment with drugs like sildenafil, prostacyclin, nitric oxide, extracorporeal membrane oxygenation and advanced modes of mechanical ventilation, about 4 to 33% of the affected infants still die and those who survive might struggle with long and major term sequelaes like chronic lung disease, seizures and neurodevelopmental problems [6,8].

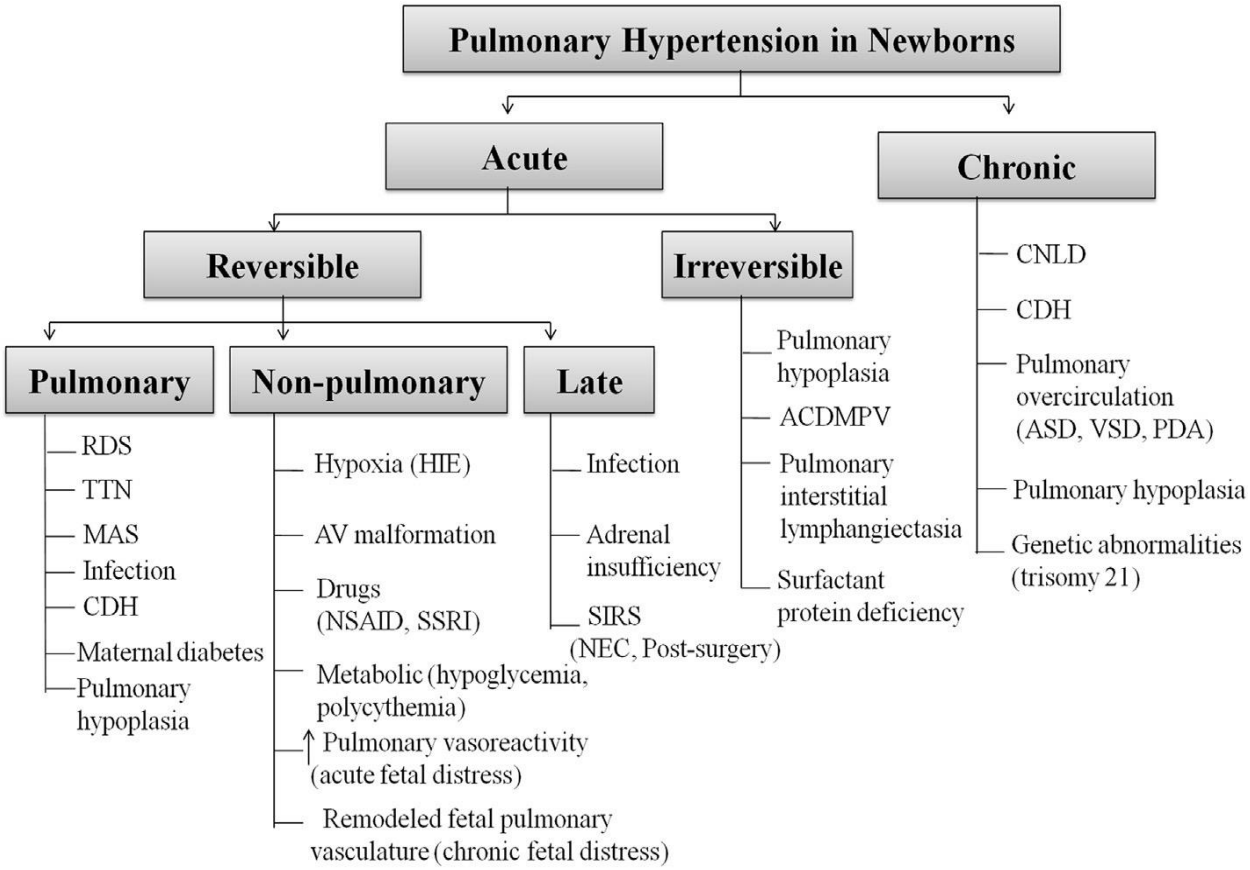

Figure1: Pulmonary hypertension in neonates can be classified as acute or chronic and may arise from a variety of underlying disorders. RDS, respiratory distress syndrome; TTN, transient tachypnea of newborn; MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; HIE, hypoxiceischemic encephalopathy; AV, arteriovenous; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitors; SIRS, systemic inflammatory response syndrome; NEC, necrotizing enterocolitis; ACDMPV, alveolar capillary dysplasia with misalignment of pulmonary veins; CNLD, chronic neonatal lung disease; CDH, congenital diaphragmatic hernia; ASD, atrial septal defect. [3]

Current study was aim to focus on pulmonary hypertension and mostly on Persistent pulmonary hypertension of the newborn (PPHN). In addition to evaluate the diagnostic procedures, and treatment intervention, and before all that we intended to discuss the pathophysiology of PPHN.

2. METHODOLOGY

Electronic search was conducted through famous medical databases; PubMed/Midline, and Embase, searching literature on Persistent pulmonary hypertension of the newborn (PPHN), we searched studies that were published in English language only, and up to December,2016 and with only human subjects. Moreover, we searched the references lists of each identified article for more relevant studies.

3. RESULTS

- ***Fetal Circulation:***

Flow in the fetus is defined by high PVR and low SVR. The placenta is the site of gas exchange. Pulmonary blood circulation to fluid-filled lungs is low (roughly 8-10% of combined ventricular output in an ovine fetus) [3]. However, more recent human fetal Doppler flow research studies show a much greater lung blood circulation (13% of combined ventricular output at 20 weeks' pregnancy, increasing to 25% at 30 weeks and 21% at 38 weeks) [9].

Various factors add to the high pulmonary vascular tone in-utero, such as mechanical factors (compression of the little lung arterioles by the fluid-filled alveoli and a lack of rhythmic distension), the presence of low-resting alveolar and arteriolar oxygen tensions, and a relative absence of vasodilators [10]. Low oxygen stress and elevated levels of vasoconstrictor conciliators such as endothelin-1 (ET-1) and thromboxane play an important function in preserving raised fetal PVR [10]. Serotonin increases fetal PVR [11] and the use of serotonin re-uptake inhibitors (SSRI) during pregnancy has been connected with increased occurrence of PPHN [11].

Endothelin-1 manufactured by vascular endothelial cells is a powerful vasoconstrictor and acts through 2 receptors; ETA and ETB (**Figure 2**) [4]. The ETA receptor plays a crucial function in vasoconstriction while the ETB receptor plays a substantial function in vasodilation. Selective blockade of the ETA receptor triggers fetal pulmonary vasodilation [12]. Vasoconstriction induced by ET-1 is mediated by calcium [13]. Lung vasodilation to ETB receptor stimulation is mediated by endothelium-derived nitric oxide (NO) [13].

Vasoconstriction in response to low oxygen stress contributes to high PVR in the fetal lamb as it approaches term [14]. Basal production of vasodilator representatives such as prostacyclin (PGI2) and NO are low in the fetus. Reaction to NO depends on activity of its target enzyme, soluble guanylate cyclase (sGC). In the ovine fetus (term gestation is 145-147d), sGC mRNA levels are low during early preterm pregnancy (126d) and considerably boost during late preterm and early term gestation (137d) [15]. There is abundant sGC activity in the lung at late pregnancy and the early newborn period and slowly reduces in adult rats [16] Low levels of pulmonary arterial sGC activity throughout late canalicular and early saccular phases of lung advancement are likely responsible for the poor response to inhaled nitric oxide (iNO) observed in preterm infants < 29 weeks GA [17].

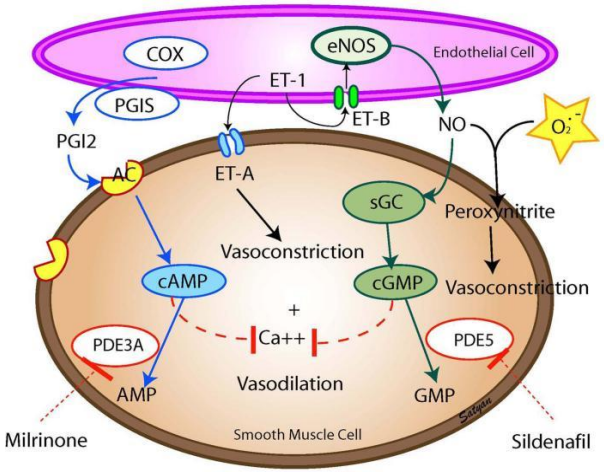

Figure 2: Endothelium derived vasodilators – prostacyclin (PGI2) and nitric oxide (NO) and vasoconstrictor (endothelin, ET-1). The enzymes, cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). [4]

- ***Pathophysiology and etiology of PPHN:***

There is proof recommending that an alteration of the NO pathway adds to PPHN. Activity and expression of eNOS and sGC in lungs is decreased [18,19] in the fetal lamb design of PPHN. In these lambs, the vascular action to NO itself is also lessened, [20] whereas the response to cGMP is regular. Thus the decreased responsiveness appears to result from reduced vascular smooth muscle sensitivity to NO at the level of sGC. Decreased expression of eNOS [21] and minimized levels of NO metabolites in urine [22] have actually also been kept in mind in infants with PPHN.

Endothelin-1 through ETA stimulation is thought to contribute to the pathogenesis of PPHN. ET-1 production is increased [23] in the lungs in the fetal lamb model of PPHN. Chronic intrauterine ETA receptor blockade following ductal ligation reduces right ventricular hypertrophy and distal muscularization of small pulmonary arteries and increases the fall in PVR at shipment in newborn lambs with PPHN [24]. ET-1 has been revealed to decrease eNOS expression and activity through ETA receptor-mediated generation of hydrogen peroxide [25]. In addition to hydrogen peroxide, superoxide, another reactive oxygen types, may trigger lung vasoconstriction and contribute in the pathogenesis of PPHN. Superoxide might scavenge NO and disrupt its signaling path. In the fetal lamb design of PPHN, increased superoxide levels have actually been shown in the pulmonary arteries [26].

The etiology of PPHN can be classified into 3 main categories (**Table 1**) [27]. The most common one is the PPHN secondary to parenchymal diseases including meconium goal syndrome (MAS), severe respiratory distress syndrome) RDS and pneumonia. This is generally due to poor oxygen entry into the alveolar space, especially in MAS with obstruction in the air passages. Insufficient capillary density with reduced overall random sample of lung vasculature and increased lung vascular resistance is the cause of PPHN in hereditary diaphragmatic hernia. The least typical etiology is typical parenchyma with renovated lung vasculature such as idiopathic PPHN, congenital heart disease, and chronic intrauterine hypoxia. Some congenital heart diseases are connected with obstructed lung venous return which can cause secondary increased pulmonary artery resistance. Hypoxic-ischemic encephalopathy due to chronic intrauterine hypoxia may remodel the pulmonary vasculature with either eNOS uncoupling or increased ET-1 production that increases pulmonary vascular resistance [28]. Idiopathic PPHN is the rarest reason for PPHN normally with regular chest x-ray findings. There are some metabolic, or hereditary, conditions that can present with PPHN. Pearson et al reported heterozygote T1405N genotype for carbamoyl-phosphotate synthatase, an enzyme that figure out the blood levels of arginine and citrulline, is connected with PPHN possible due to absence of substrate for endothelial nitric oxide synthase (eNOS) [28]. Epidemiologic research study demonstrated black and Asian maternal race is connected with substantial higher risk for PPHN. Male gender also leads to greater occurrence of PPHN [29].

Table1: Classification of PPHN [27]

•	**A**bnormally constricted pulmonary vasculature due to parenchymal diseases
○	■ meconium aspiration syndrome
○	■ respiratory distress syndrome
○	■ pneumonia
•	Hypoplastic pulmonary vasculature
○	■ congenital diaphragmatic hernia
○	■ lung hypoplasia
•	Normal parenchyma with remodeled pulmonary vasculature
○	■ idiopathic PPHN
○	■ congenital heart disease
○	■ Hypoxic-ischemic encephalopathy, chronic

- ***Diagnosis of PPHN:***

Classically, diagnosis of PPHN is medically believed in neonates providing with signs of breathing distress and HRF during the first few days of age, particularly when it occurs in the context of incriminating clinical history. Certainly, PPHN occurs more regularly secondary to an underlying etiology [3]. A cautious appraisal of the medical situation, that includes careful extraction of a comprehensive case history and conclusion of a comprehensive scientific assessment, may offer crucial etiological hints. Medical evaluation will normally need to be quick and performed alongside resuscitative procedures to ensure prompt stabilization. For example, a history of fetal distress, severe metabolic acidosis in cord blood, low Apgar ratings and/or the presence of meconium in amniotic fluid and/or in the neonate's throat visualized on direct laryngoscopy in addition to normal chest X-ray findings suggest a substantial perinatal hypoxic ischemic event or series of events. Meconium aspiration syndrome may also occur in the setting of considerable perinatal asphyxia; history of extended rupture of membranes, group B streptococcus colonization, or presence of chorioamnioitis recommend infection. In addition to the clinical features of septic shock or the existence of bronchopneumonia on chest radiograph, blood, urine or cerebrospinal fluid testing may expose evidence of intense systemic inflammation [3,4].

Strategies such as cardiac catheterization and MRI for assessment of pulmonary vascular resistance, blood circulation and myocardial function are currently not practical in an ill newborn. Echocardiography is the only currently practical bedside clinical investigation and is consistently used to verify the diagnosis of PPHN and to keep track of disease progression or reaction to treatments. It is an easy, noninvasive, bedside test, which can be carried out even in the most unstable patients. For older children and grownups, PHT is generally identified by echocardiography if pulmonary artery peak systolic pressure is > 35 mmHg (30). This definition might be helpful for infants with late-onset, chronic or intense PHT, it is not suitable for detecting acute PPHN during the early neonatal period. This is since even under physiological conditions, pulmonary pressures are expected to be high at birth and decline thereafter. The decrease is likely to be most fast over the very first couple of hours to days of age [31]. A variety of echocardiography indices of PVR and PHT have actually been validated in adult patients [32,33]. Enhancements in imaging methods and wide dissemination of echocardiography equipment permit timely evaluation of these indices in neonates; yet their clinical usage in PPHN is limited by the relative paucity of normative neonatal information [33].

- ***Treatment approaches of PPHN:***

General approach:

For neonates providing with HRF after birth, early recognition of signs, timely resuscitation, close post-resuscitation monitoring, and appropriate escalation of cardiorespiratory interventions are vital management actions prior to starting a trial of specific lung vasodilator treatments. In some patients, resolution of HRF might take place without the need for more escalation of treatment [3,4]. The resuscitation ought to be supplied utilizing the sequential 'airway ebreathingecirculation' method as recommended in standard neonatal resuscitation algorithms. Most of neonates with substantial PPHN are anticipated to require invasive ventilatory assistance. Whereas a brief trial of non-invasive ventilation may be acceptable, close clinical tracking is necessary to guarantee prompt escalation. The ventilation method should be focused to develop sufficient alveolar recruitment and carbon dioxide clearance while avoiding lung hyper-expansion. This may require escalation to high-frequency modes of ventilation and ought to be confirmed and followed with chest radiograph and arterial blood gas. The goal of circulatory evaluation is to ascertain adequacy of systemic perfusion and to titrate treatments appropriately. Non-specific but regularly kept an eye on medical functions suggestive of insufficient systemic blood flow consist of prolonged capillary filling time, low pulse volume, and systolic hypotension; the existence of continual metabolic acidosis due to high arterial lactate is a rather specific sign of decreased tissue oxygen shipment. Establishment of protected venous and arterial gain access to is vital. Antibiotic treatment, if suggested, should be started at the earliest chance. Pre- and post-ductal pulse oximetry monitoring should be initiated to keep an eye on the magnitude and evaluate of any right-to-left ductal shunt along with the possibility of cyanotic CHD. The oxygenation index (OI) ought to be determined, if feasible, to assess and document the seriousness of oxygenation failure. Neonates in whom HRF continues spite of establishing appropriate ventilation and circulatory resuscitation in the lack of CDH with an OI of > 15 are thought about candidates for trial of specific pulmonary vasodilator treatment [3].

Oxygen therapy for PPHN*:*

The target oxygen concentration ideal for optimizing results for neonates with PPHN is not established. Typically, clinicians have intended to maintain above-normal oxygen material while managing babies with PPHN, presumably prompted by the discovery of oxygen as an essential mediator in the physiological drop in PVR at birth and the fact that hypoxia causes a vasoconstrictor action in the pulmonary vascular bed. The usage of oxygen to remedy hypoxia and lessen hypoxic lung vasoconstriction are crucial medical goals in managing neonates with PPHN, keeping greater than normal blood oxygen content has actually not been scientifically shown to provide any extra benefits, and might be possibly harmful [34]. The relationship in between PVR and arterial partial pressure of oxygen (PaO2) has actually been investigated in a variety of experiments utilizing neonatal animal designs. In 1966, Rudolph and Yuan measured PVR and lung arterial pressure utilizing intrusive techniques in normal newborn calves as PaO2 was slowly reduced from 100 mmHg [35]. Surprisingly, PVR stayed low and did not alter throughout a variety of PaO2 worths in between 50 and 100 mmHg. More decreases in PaO2 < 50 mmHg lead to a rapid increase in both PVR and suggest pulmonary arterial pressure. These findings were reconfirmed in a recent experiment in typical newborn lambs [36]. In addition, the relationship in between PVR and PaO2 at birth remained unchanged even when PPHN was induced experimentally by intrauterine ductal ligation [37]. Further, studies in the very same design showed that prior exposure to hyperoxia led to exaggerated pulmonary vasoconstriction after a hypoxic insult and blunted vasodilatory impacts of iNO. Treatment with recombinant superoxide dismutase reversed this impact, recommending a function of oxygen totally free radicals [38]. In

addition, oxygen free radicals have been revealed to connect with iNO producing peroxynitrite, an NO metabolite that is linked in moderating lung vasoconstriction and ideal ventricular dysfunction [39]. Offered the current state of proof, avoidance of both hypoxia and hyperoxia, and maintenance of oxygen levels within physiologically typical variety (PaO2 in between 60 and 100 mmHg) seem the safest and most appropriate medical techniques in neonates with PPHN.

Surfactant treatment of PPHN:

A multi-centre placebo-controlled trial [40] showed that, in infants with extreme respiratory failure born at term, early use of surfactant substantially decreased the need for ECMO. The infants consisted of in the study were greater than 36 weeks of gestational age and had meconium aspiration syndrome, PPHN or sepsis.

Management of PPHN by Vasodilators:

Tolazoline is a potent non-specific vasodilator, which acts mostly as a competitive a-adrenergic villain. It is not effective in all infants with PHN; in an early research study [41] oxygenation enhanced in just 67% of the infants with extreme lung disease treated with intravenous tolazoline. There is a high rate (82%) of side-effects, particularly systemic hypotension, gastrointestinal haemorrhage and kidney failure. It is possible that certain of the negative results might be averted by concomitant administration of a volume expander and by offering the tolazoline by a sluggish bolus infusion; the evidence, nevertheless, is from a non-controlled series (42). An option method of trying to prevent the unwanted systemic effects is to provide tolazoline straight into the lungs. Small unrestrained research studies in infants [43,44] have highlighted the fact that administration of tolazoline via the endotracheal tube can enhance oxygenation without negative effects. The dose utilized, nevertheless, may be important; too big a dose might imply 'overflow' into the systemic circulation [44].

Prostacyclin (PGI2) produces vasodilation through the production of cyclic adenine monophosphate (cAMP). In a small, unchecked study [45], PGI2 infusion resulted in a reduction in the mean pulmonary artery pressure from 68.6 to 49.6 mmHg; the infusion was begun after volume correction and inotropic medication. Systemic administration of PGI2, however, might also cause hypotension and alternative techniques of shipment have been explored. Preliminary data recommend that nebulised PGI2 might improve oxygenation without side-effects, however only four infants were studied [46].

4. CONCLUSION

PPHN is a prevalent neonatal issue whose trademark medical function is oxygenation failure, yet it represents a spectrum of physiologic factors that need to be considered when making medical choices. Neonatal intensivists must recognize and follow the basic therapeutic method consisting of the judicious use of oxygen, the administration of Inhaled nitric oxide (iNO) and accomplishment of suitable lung recruitment. It is equally essential not to forget the fundamental physiologic reasoning, which forms the basis of this method and is based on management of elevated PVR. When thinking about alternative pulmonary vasodilators or drugs to support best ventricular performance, the latter is most pertinent.

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