Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment

Amish Jain, Patrick J. McNamara

Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada
Division of Neonatology, Hospital for Sick Children, Toronto, Ontario, Canada
Departments of Pediatrics and Physiology, University of Toronto, Toronto, Canada

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SUMMARY

Persistent pulmonary hypertension of the newborn (PPHN) is a frequent cause for admission to the neonatal intensive care unit and is associated with mortality and variable morbidities. It is primarily a state of oxygenation failure representing a failure of the normal postnatal decline in pulmonary vascular resistance that may be associated with right ventricular dysfunction. Enhanced knowledge of the pathophysiologic contributors to this syndrome helps clinicians understand its phenotypic expression and facilitates more focused intensive care decision-making. The approach to treatment should be based on alleviation of the elevation in pulmonary vascular resistance and should include optimization of lung recruitment and judicious use of pulmonary vasodilators. When response to inhaled nitric oxide is suboptimal, the physiologic contributors to impaired oxygenation need further investigation. Targeted neonatal echocardiography provides novel physiologic insights; in particular, it may help assess the adequacy of right ventricular performance, the relative contribution of the fetal shunts and the magnitude of the overall impairment to cardiac output. This information may facilitate therapeutic next steps and whether adjunctive vasodilators or drugs to augment ventricular function are preferable. This article provides a comprehensive overview of the pathological contributors to PPHN, the physiologic constituents of its phenotypic expression, standard approach to therapeutic intervention, and the role of bedside echocardiography in enhancing the decision-making process.

1. Introduction

Pulmonary hypertension (PHT) is a serious cardiopulmonary disorder characterized by elevated mean pulmonary artery pressure (mPAP) and prolonged exposure of the right ventricle to high afterload. Physiologically, mPAP is directly related to pulmonary blood flow (PBF), pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP) by the equation:

\[ \text{mPAP} = \frac{\text{PBF} \times \text{PVR}}{\text{PCWP}} + \text{PCWP}. \]

Although PHT may result from high PBF (e.g., large left-to-right shunts, severe chronic anemia) or rise in PCWP (e.g., left ventricular dysfunction), the vast majority of cases are secondary to high PVR. In neonates, PHT is almost always secondary to dysregulation of PVR. PHT is a frequent diagnosis in tertiary neonatal intensive care units and may arise secondary to a wide range of diseases. Broadly, PHT in neonates can be described as acute or chronic (Fig. 1), which are distinguished by intrinsic differences in their pathophysiology and clinical presentation [1]. While acute episodes of neonatal PHT may occur later in neonatal illnesses (e.g., secondary to sepsis), the most usual presentation is in the immediate postnatal period, secondary to abnormal transition of the pulmonary circulation from a high-resistance intrauterine to a low-resistance extraterine circuit. This characteristic presentation of acute pulmonary hypertensive crises is widely referred to as persistent pulmonary hypertension of the newborn (PPHN). Chronic PHT, on the other hand, occurs due to secondary rise in PVR following initial successful postnatal transition, and is seen most frequently as a secondary complication of chronic neonatal lung disease in prematurely born neonates [2,3]. The majority of research in neonatal PHT has focused on PPHN, yet knowledge gaps remain and core physiologic...
concepts are oftentimes neglected; in addition, the relative contribution of chronic PHT to adverse clinical outcomes is just beginning to be realized.

Persistent pulmonary hypertension of the newborn is one of the most challenging acute disorders of postnatal transition with substantial morbidity and mortality. Perinatal asphyxia, meconium aspiration syndrome and sepsis account for the majority of cases; irreversible causes are fortunately rare. Occasionally, PPHN may be the primary diagnosis when no other underlying pathology can be identified. Although improved obstetric care has considerably reduced the incidence of these perinatal pathologies, PPHN continues to be an important clinical problem accounting for up to 4% of all admissions to some tertiary neonatal units. The incidence in developed countries ranges from one to two per 1000 live births with a mortality rate of ~10% [4,5]. Surviving neonates often require prolonged cardiorespiratory support, have a long hospital stay, and are at high risk of long-term adverse neurodevelopmental outcomes [6]. Although inter-pathway interactions exist and relationships may be complex in nature, for the sake of simplicity, the relevant pathways could be described under following headings: (A) nitric oxide (NO)-soluble guanylate cyclase (cGMP); (B) prostaglandin—prostacyclin—cyclic adenosine monophosphate (cAMP); (C) endothelin; (E) free radicals. Among these pathways, pathways (A), (B) and (D) have been the subjects of most interest. Oxygen and NO represent mediators of pulmonary vasodilatation translated into standard clinical practice. Unfortunately, a number of other mediators have been identified, prompting the development of adjunctive/alternate therapeutic agents. Whereas successful use of many alternate therapeutic agents have been described in PPHN, the relative contributory role of each mediator in enabling successful physiological transition after birth and under pathological conditions has not been completely elucidated. Pulmonary vasodilatation has been shown to occur in response to stimulation by nitric oxide (NO) [7], prostacyclin (PGI2) [9,10] and soluble guanyl cyclase (SGC) [11] and inhibition of phosphodiesterase 3 and/or 5 (PDE 3/5) [12–14], endothelin 1 (ET 1) [15,16], reactive oxygen species (ROS) [17], and rho-kinase [18,19]. A basic knowledge of these regulatory pathways and target mediators is necessary for clinicians involved in the management of PPHN as an essential prerequisite of the clinical decision-making process.

2. Pathophysiology

2.1. Cellular pathways

Several cellular pathways involved in regulation of pulmonary vascular tone have been identified over the last two decades [1,8]. It is important for clinicians to be aware of these pathways, which modulate pathophysiologic progression and clinical impact. Although similarities exist and relationships may be complex in nature, the relevant pathways could be described under following headings: (A) nitric oxide (NO)-soluble guanylate cyclase—cyclic guanyl monophosphate (cGMP); (B) prostaglandin—prostacyclin—cyclic adenosine monophosphate (cAMP); (C) rho-A/rho-kinase; (D) endothelin; (E) free radicals. Among these pathways, pathways (A), (B) and (D) have been the subjects of most interest. Oxygen and NO represent mediators of pulmonary vasodilatation translated into standard clinical practice. Subsequently, a number of other mediators have been identified, prompting the development of adjunctive/alternate therapeutic agents. Whereas successful use of many alternate therapeutic agents have been described in PPHN, the relative contributory role of each mediator in enabling successful physiological transition after birth and under pathological conditions has not been completely elucidated. Pulmonary vasodilatation has been shown to occur in response to stimulation by nitric oxide (NO) [7], prostacyclin (PGI2) [9,10] and soluble guanyl cyclase (SGC) [11] and inhibition of phosphodiesterase 3 and/or 5 (PDE 3/5) [12–14], endothelin 1 (ET 1) [15,16], reactive oxygen species (ROS) [17], and rho-kinase [18,19]. A basic knowledge of these regulatory pathways and target mediators is necessary for clinicians involved in the management of PPHN as an essential prerequisite of the clinical decision-making process.
In looking after neonates with PPHN, particularly when standard therapeutic measures do not succeed.

### 2.2. Hemodynamics

Irrespective of the underlying etiology or cellular pathways, high PVR is the hallmark pathophysiological feature in PPHN. Although the hemodynamic and clinical consequences may be similar between patients, it is important to recognize the potential for variability in phenotypic presentation according to the presence or absence of fetal shunts and the ability of the myocardium to adapt to alterations in cardiac loading conditions. In many patients, the consequences may include a vicious cycle of reduced pulmonary blood flow (PBF), hypoxemia, acidosis, ventilation-perfusion mismatch, and cardiac dysfunction (Fig. 3). Although these hemodynamic disturbances are well appreciated in PPHN, their specific contribution to the clinical phenotype is poorly understood. The type and severity of secondary hemodynamic disturbances may vary among patients depending upon the severity and duration of the primary problem (i.e., high PVR) as well as underlying etiology.

Significant pulmonary vasoconstriction, even in the absence of other secondary hemodynamic alterations, can produce the clinical picture of hypoxic respiratory failure (HRF) by causing severe ventilation-perfusion mismatch, and cardiac dysfunction (Fig. 3). Although these hemodynamic disturbances are well appreciated in PPHN, their specific contribution to the clinical phenotype is poorly understood. The type and severity of secondary hemodynamic disturbances may vary among patients depending upon the severity and duration of the primary problem (i.e., high PVR) as well as underlying etiology.

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leftward deviation of the interventricular septum, thereby reducing the left ventricular filling capacity and compliance. Systolic dysfunction of the right ventricle, by virtue of ventricular–ventricular interaction through shared myocardial fibers between the two ventricles, may adversely affect LV systolic function [20]. Further, non-PVR related factors might also contribute to the myocardial dysfunction. These factors include the underlying etiology (e.g. sepsis, perinatal asphyxia), systemic hypovolemia, invasive ventilation with high mean airway pressure and medications (e.g. pulmonary vasoconstriction from high-dose epinephrine and dopamine, low preload secondary to systemic vasodilatation from milrinone) [21]. Furthermore, the role of fetal shunts needs thoughtful consideration. A large PDA, if present, may shunt blood from the pulmonary to systemic circulation; on one hand, this may protect the neonatal right ventricle by offloading the high-resistance pulmonary circuit and support postductal systemic perfusion, but may also potentiate hypoxemia by promoting low PBF. Similarly the presence of a right-to-left transatrial shunt may support preductal cardiac output and cerebral perfusion when pulmonary venous return and left heart preload are severely compromised, but at the expense of lower blood oxygenation. The merits/harm of fetal channels need broad consideration according to the unique pathophysiological circumstances. Regardless, if uncorrected, the clinical picture in PPHN may rapidly progress to a state of refractory hypoxemia and severe systemic hypoperfusion and shock.

2.3. Right ventricular performance and PPHN

The right ventricle plays an essential role in supporting pulmonary blood flow during the normal neonatal transition. The ability of the right ventricle to maintain or augment its performance in the setting of PPHN, where there is failure of the normal postnatal decline in PVR, is an important component of the adaptive response. In the setting of impaired RV systolic performance, relatively small increases in PVR may have a deleterious effect on both pulmonary blood flow and recoverability of normal function. Little attention is paid to the adequacy of RV performance when considering therapeutic options. RV dysfunction may result from any structural or functional process, decreasing the ability of the right ventricle to pump blood into the pulmonary circulation. The usual causes include alterations in preload and/or diastolic filling, direct impairment of myocardial performance due to hypoxic–ischemic and/or a septic insult, and increases in RV afterload (Fig. 4). RV preload and diastolic filling affect myocardial fiber length and contractility via the Frank–Starling mechanism; both increases as well as decreases in preload may negatively affect RV function. The most frequent causes of RV dysfunction in the neonatal period are pulmonary hypertension (PH), acute lung injury, birth asphyxia, sepsis, secondary to impaired LV performance and post-cardiothoracic surgery states. Arrhythmias and pericardial, congenital, and/or valvular heart disease may also contribute. The pathophysiology of acute RV dysfunction in critically ill adult patients is complex and may include ischemia, endotoxin, and cytokine-induced decreases in systolic and diastolic LV and RV function, as well as afterload increases from hypoxic pulmonary vasoconstriction (HPV) [22–24]. There are few neonatal data on this subject matter, although similar mechanisms would appear to be biologically plausible. Left ventricular dysfunction induces RV dysfunction via afterload increase, and/or displacement of the interventricular septum toward the right ventricle with subsequent impairment of RV filling. Hypovolemia and inflammation-induced capillary leak alter RV function by decreasing preload. Mechanical ventilation, certain drugs, and volume overload may further alter RV function. An understanding of the pathological contributors to and physiologic consequences of impaired RV function will enable an enhanced approach to therapeutic intervention.

![Fig. 4. Physiologic approach to the management of impaired right ventricular function. RV, right ventricle; SVC, superior vena cava; HIE, hypoxic–ischemic encephalopathy; MI, myocardial infarction; LV, left ventricle.](image-url)
3. Clinical evaluation and diagnosis

Classically, diagnosis of PPHN is clinically suspected in neonates presenting with signs of respiratory distress and HRF during the first few days of age, especially when it occurs in the context of incriminating clinical history. Indeed, PPHN occurs more frequently secondary to an underlying etiology. A careful appraisal of the clinical scenario, which includes careful elicitation of a detailed case history and completion of a thorough clinical examination, may provide important etiological clues. Clinical assessment will usually have to be quick and performed alongside resuscitative measures to ensure timely stabilization. For example, a history of fetal distress, severe metabolic acidosis in cord blood, low Apgar scores and/or the presence of meconium in amniotic fluid and/or in the neonate’s larynx visualized on direct laryngoscopy along with typical chest X-ray findings suggest a significant perinatal hypoxic–ischemic event or series of events. Meconium aspiration syndrome may also occur in the setting of significant perinatal asphyxia; history of prolonged rupture of membranes, group B streptococcus colonization, or presence of chorioamnionitis suggest infection. In addition to the clinical features of septic shock or the presence of bronchopneumonia on chest radiograph, blood, urine or cerebrospinal fluid testing may reveal evidence of acute systemic inflammation. A history of elective cesarean section and radiological finding of fluid in interlobar fissures suggests transient tachypnea of the newborn. Other, relatively less frequent etiologies include respiratory distress syndrome, especially in late-preterm and term neonates born to mothers with poorly controlled diabetes; antenatal drug exposure (e.g. delayed transition from selective serotonin reuptake inhibitors, antenatal closure of ductus arteriosus from non steroidal anti-inflammatory drugs); chromosomal anomalies; pulmonary hypoplasia (secondary to congenital diaphragmatic hernia or severe long standing oligohydramnios). A family history positive for previous neonatal deaths from respiratory failure and/or a history of consanguinity may point towards surfactant protein deficiency. A neonate who appeared well at birth with normal Apgar scores but presents minutes or hours later with severe respiratory distress and HRF which is relatively unresponsive to medical management may suggest alveolar capillary dysplasia with misalignment of pulmonary veins, a rare genetic disorder characterized by maldevelopment of the capillary vascular bed around the alveoli in the lungs. Enhanced appreciation of the likely etiology may enable a more focused and disease-specific approach to therapeutic interventions. This is highly relevant for unique situations such as hypoxic–ischemic encephalopathy where the benefits of therapeutic hypothermia in minimizing the risk of brain injury need to be carefully balanced against the resultant aggravation of PVR. Regardless, therapeutic hypothermia is a post-stabilization intervention.

Establishing the relative contribution of parenchymal lung disease versus high PVR to the clinical picture of HRF can be challenging, especially as they often coexist. The clinical features which suggest high PVR as the major contributor include severity of oxygenation failure characterized by an oxygenation index of >25% despite optimization of lung recruitment, presence of lability of systemic oxygenation and a pre-to-post ductal saturation difference of >10% on pulse oximetry (SpO2). Adequacy of invasive ventilation may be judged according to arterial partial pressure of carbon dioxide, qualitative assessment of lung expansion/aeration on chest radiograph and failure of improvement in oxygenation independent of appropriate increases in mean airway pressure. Oxygen lability refers to the clinical observation of decrements in oxygenation associated with agitation or handling and is suggestive of excessive pulmonary vaso-reactivity. Continuous pre-to-post ductal SpO2 monitoring is a widely used investigation to screen for and monitor treatment response in PPHN patients with a patient ductus arteriosus. Higher pre-than post-ductal SpO2 values relate to increased shunting of blood from the main pulmonary artery to descending aorta through a patent ductus arteriosus (PDA) and indicate higher PVR in comparison to systemic vascular resistance (SVR). It is important that pre-ductal SpO2 is measured in the right upper limb and post-ductal in one of the lower limbs, as the arterial supply to the left arm may be either pre- or post-ductal in origin. Although a positive screen is strongly suggestive of PPHN, negative screen does not rule it out since the ductus arteriosus may not be patent [25,26]. Further, clinicians should be aware that left-sided obstructive heart defects (coarctation of aorta; interrupted aortic arch; hypoplastic left heart syndrome) might demonstrate a ‘false’ positive screen and that treatment strategies aimed to lower PVR may cause clinical deterioration in these patients.

3.1. Role of echocardiography in diagnosing PPHN

Techniques such as cardiac catheterization and MRI for assessment of pulmonary vascular resistance, blood flow and myocardial function are currently not feasible in a sick newborn. Echocardiography is the only presently feasible bedside clinical investigation and is routinely used to confirm the diagnosis of PPHN and to monitor disease progression or response to therapies. It is a simple, non-invasive, bedside test, which can be performed even in the most unstable patients. For older children and adults, PHT is usually diagnosed by echocardiography if pulmonary artery peak systolic pressure is > 35 mmHg [27]. Although this definition may be useful for infants with late-onset, acute or chronic PHT, it is not applicable for diagnosing acute PPHN during the early neonatal period. This is because even under physiological conditions, pulmonary pressures are expected to be high at birth and decline thereafter. The decline is likely to be most rapid over the first few hours to days of age [28]. A number of echocardiography indices of PVR and PHT have been validated in adult patients [29,30]. Enhancements in imaging techniques and wide dissemination of echocardiography equipment allow timely assessment of these indices in neonates; yet their clinical use in PPHN is limited by the relative paucity of normative neonatal data. Re-characterization of normal transitional physiology using echocardiography in a time-sensitive manner during early postnatal period can further inform its scientific use in management of neonates with PPHN. Nevertheless, echocardiographic findings consistent with suprasystemic pulmonary pressures, if present, are considered diagnostic of PPHN. The most widely used measurements include peak systolic RV pressure calculated from measured velocity of tricuspid regurgitant jet, presence of pure right-to-left shunt at the ductal or atrial level, and paradoxical interventricular septal motion at end-systole. On the other hand, findings suggestive of high pulmonary pressures at levels which are not suprasystemic, such as bidirectional shunts or flat interventricular septal motion, should be considered supportive at best, of diagnosis of PPHN, especially when interpreted in context of the clinical symptoms. It should be noted that presence of significant RV systolic dysfunction may lead to underestimation and false ‘normalization’ of many echocardiographic indices of PHT which are pressure dependent – hence the importance of paying more attention to and developing enhanced methods of qualitative and quantitative evaluation of RV systolic function in neonates with PPHN.

3.2. Congenital heart defect versus PPHN

Timely evaluation, to rule out a critical cyanotic congenital heart defect (CHD), is of critical importance for neonates suspected to have PPHN. The possibility of a duct-dependent pulmonary blood flow disorder should be considered in all neonates presenting with
HRF during the neonatal period, particularly when symptoms fail to resolve after resuscitation and standard treatment [31]. Delays in establishment of the correct diagnosis and implementation of appropriate treatment may worsen prognosis [32]. The clinical factors which may point towards critical cyanotic CHD include: family history, relative absence of signs of respiratory distress, presence of cardiovascular findings such as murmur, weak lower limb pulsations, abnormal heart shape on chest radiograph and abnormal electrocardiograph, relatively fixed SpO2, absence of systemic hypotension in spite of severe prolonged hypoxemia, presence of reverse differential cyanosis (i.e., post-ductal SpO2 > pre-ductal by ≥ 10%) as it may indicate right-to-left shunting of oxygenated blood across PDA [e.g., total anomalous pulmonary venous connections (TAPVC), transposition of great arteries], ‘failed’ hyperoxia test and failure to respond to or worsening with vasodilator therapies. Although these clinical features may provide important clues regarding underlying etiology, their inherent sensitivity and specificity remain low. The hyperoxia test has been widely accepted in clinical practice, but may also be equivocal in the setting of critically low FiO2 due to severe PPHN. Further, PPHN is known to be an associated finding at presentation of certain critical CHDs, making clinical distinction even more difficult. As referred to, avoidance of therapeutic strategies. The reduced PVR may compromise patients with certain forms of heart defects, particularly disorders associated with excessive pulmonary blood flow (e.g., TAPVC; double outlet right ventricle) or duct-dependent systemic blood flow lesions (e.g., hypoplastic left heart syndrome), although this list is not absolute. A comprehensive structural echocardiography assessment performed by an experienced operator is the only accepted definitive test in routine clinical practice. Ideally all cases suspected of PPHN should have an echocardiogram as soon as possible to confirm the diagnosis and rule out CHD; unfortunately 24/7 echocardiography services and pediatric cardiology expertise are not available in many centers and hospitals. It is our opinion that patients with a presumptive diagnosis of PPHN, where HRF continues in spite of standard treatment or where the likelihood of duct-dependent CHD is considered high, require urgent evaluation by an experienced pediatric cardiologist. If delays in cardiology consultation are anticipated or illness severity is high, it may be desirable to maintain ductal patency by intravenous infusion of prostaglandins until a diagnosis is reached.

4. Management

4.1. General approach

For neonates presenting with HRF after birth, early identification of symptoms, timely resuscitation, close post-resuscitation monitoring, and appropriate escalation of cardiorespiratory interventions are essential management steps prior to embarking on a trial of specific pulmonary vasodilator therapies. In some patients, resolution of HRF may ensue without the need for further escalation of treatment. The resuscitation should be provided using the sequential ‘airway—breathing—circulation’ approach as recommended in standard neonatal resuscitation algorithms. The majority of neonates with significant PPHN are expected to require invasive ventilatory support. Whereas a short trial of non-invasive ventilation may be acceptable, close clinical monitoring is essential to ensure timely escalation. The ventilation strategy should be focused to establish adequate alveolar recruitment and carbon dioxide clearance while avoiding lung hyper-expansion. This may require escalation to high-frequency modes of ventilation and should be confirmed and followed with chest radiograph and arterial blood gas. The goal of circulatory assessment is to ascertain adequacy of systemic perfusion and to titrate treatments accordingly. Non-specific but frequently monitored clinical features suggestive of inadequate systemic blood flow include prolonged capillary filling time, low pulse volume, and systolic hypotension; the presence of sustained metabolic acidosis due to high arterial lactate is a rather specific sign of decreased tissue oxygen delivery. Establishment of secure venous and arterial access is essential. Antibiotic treatment, if indicated, should be initiated at the earliest opportunity. Pre- and post-ductal pulse oximetry monitoring should be initiated to assess and monitor the magnitude of any right-to-left ductal shunt as well as the possibility of cyanotic CHD. The oxygenation index (OI) should be calculated, if feasible, to assess and document the severity of oxygenation failure. Neonates in whom HRF persists in spite of establishing adequate ventilation and circulatory resuscitation in the absence of CDH with an OI of >15 are considered candidates for trial of specific pulmonary vasodilator therapy.

4.2. Oxygen therapy

The target oxygen concentration ideal for optimizing outcomes for neonates with PPHN is not established. Traditionally clinicians have aimed to maintain above-normal oxygen content while managing babies with PPHN, presumably prompted by the discovery of oxygen as an important mediator in the physiological drop in PVR at birth and the fact that hypoxia induces a vasoconstrictor response in the pulmonary vascular bed. Although the use of oxygen to correct hypoxia and minimize hypoxic pulmonary vasoconstriction are important clinical goals in managing neonates with PPHN, maintaining higher than normal blood oxygen content has not been scientifically shown to confer any additional benefits, and may be potentially harmful [33]. The relationship between PVR and arterial partial pressure of oxygen (PaO2) has been investigated in a number of experiments using neonatal animal models. In 1966, Rudolph and Yuan measured PVR and pulmonary arterial pressure using invasive methods in normal newborn calves as PaO2 was gradually decreased from 100 mmHg [34]. Interestingly, PVR remained low and did not change across a range of PaO2 values between 50 and 100 mmHg. However, further reductions in PaO2 <50 mmHg lead to an exponential increase in both PVR and mean pulmonary arterial pressure. These findings were reconfirmed in a recent experiment in normal newborn lambs [35]. In addition, the relationship between PVR and PaO2 at birth remained unchanged even when PPHN was induced experimentally by intrauterine ductal ligation [36]. Further, studies in the same model demonstrated that prior exposure to hyperoxia led to exaggerated pulmonary vasoconstriction after a hypoxic insult and blunted vasodilatory effects of iNO. Treatment with recombinant superoxide dismutase reversed this effect, suggesting a role of oxygen free radicals [37]. Additionally, oxygen free radicals have been shown to interact with iNO producing peroxynitrite, an NO metabolite that is implicated in mediating pulmonary vasoconstriction and right ventricular dysfunction [38]. Given the current state of evidence, avoidance of both hypoxia and hyperoxia, and maintenance of oxygen levels within physiologically normal range (PaO2 between 60 and 100 mmHg) appear to be the safest and most appropriate clinical approaches in neonates with PPHN.

4.3. Standard of care

Inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) are two therapeutic options that have undergone rigorous evaluation and have scientifically proven benefits for infants with PPHN who fail to respond to ventilation and resuscitation measures [7,39]. Among various pulmonary vasodilatory therapeutic agents, iNO is the only agent approved by the
US Food and Drug Administration for use in neonates with PPHN, and, when available, should always be the first-line treatment. iNO treatment should be initiated at a dose of 20 parts per million (ppm), as it identifies the majority of ‘responsive’ cases and is rarely associated with side-effects [40]. Although some neonates may respond to doses up to 40 ppm, further escalation of the dose is not recommended as it has not been shown to provide any additional benefit and increases the risk of significant methemoglobinemia [41]. It is important to remember that iNO has only been shown to improve clinical outcomes in neonates with HRF and OI levels between 15 and 40. In clinical situations where OI remains >40 despite resuscitation and optimizing ventilatory management, it may be appropriate to try treatment with iNO but it should not delay consultation with a regional ECMO center regarding the suitability of transfer. An urgent echocardiogram to confirm diagnosis, evaluate cardiac function, and rule out cyanotic CHD is highly desirable in all neonates with persistent HRF, but is mandatory if ECMO is being considered.

4.4. Potential adjunctive treatments

Several randomized controlled trials and subsequent meta-analysis have demonstrated that treatment with iNO reduces the need for ECMO in term and near-term neonates with HRF, but without any beneficial effect on overall mortality rate and long-term morbidities [4,6,7]. In ~30–35% cases of PPHN, use of iNO is either clinically ineffective or provides only transient improvement. Additionally, the escalating cost and need for special delivery apparatus make it a non-viable option in many centers in the developing world, where both the incidence and mortality associated with PPHN is suspected to be higher. These considerations have prompted clinicians to try other alternate/adjunctive pulmonary vasodilator therapies. With the discovery of other target mediators, several therapeutic agents have been developed, many of which are used routinely in clinical practice for children and adults with PHT. Successful use of alternate drugs has been reported in management of PPHN but their efficacy and safety have not been tested in large clinical trials (Fig. 5) [8,12,19,21,27]. Further, there are no data available on the effect of these treatments on long-term neurodevelopmental outcomes. Although a short trial of alternate therapeutic agents may be justified in settings where iNO is unavailable or is ineffective, this should not delay transfer of patients to an ECMO facility for definitive management. One of the major drawbacks of these therapies is the need for systemic administration and, hence, higher potential of adverse effects. Caution should be exercised while administering systemic vasodilator therapies as it may precipitate severe hypotension, which may worsen pulmonary blood flow as well as cardiac function. Recently, successful use of inhaled prostacyclin, administered as a continuous in-line nebulization, has been described in a case series of neonates with PPHN [10]. Although this raises the possibility of selective pulmonary administration of adjunctive therapy, it requires testing in randomized trials.

4.5. Role of vasopressors in management of PPHN

One of the postulated mechanisms of HRF in neonates with PPHN is reduced PBF secondary to high PVR:SVR ratio resulting in shunting of blood away from the pulmonary circulation at the ductal level. Hence in theory, if SVR is therapeutically increased, it may reduce the PVR:SVR ratio and augment net PBF with a resultant improvement in ventilation perfusion mismatch and oxygenation. Historically, this strategy has been widely employed by clinicians when faced with clinical situations where therapies to lower PVR are unsuccessful. An ideal therapeutic agent to achieve the goal of reducing PVR:SVR ratio should increase SVR with simultaneous reduction or at least having no effect on PVR. There is animal experimental evidence that commonly used non-selective vasopressor agents such as dopamine and epinephrine may increase SVR, but are unlikely to improve PBF due to their potential vasoconstrictive effects on a labile pulmonary vascular bed [42]. the net consequence of increased PVR is unaltered or theoretically augmented PVR:SVR ratio, which would appear to be counter-intuitively clinically. A small case series evaluating the effect of norepinephrine in neonates with PPHN reported that although norepinephrine caused an increase in both PVR and SVR, the increment in PVR was relatively less pronounced, causing an overall decline in the PVR:SVR ratio which was clinically associated with improved oxygenation [43]. Another agent with properties potentially suited to alter PVR:SVR ratio in PPHN is arginine vasopressin (AVP) [44]. It primarily exerts its vasoconstrictor effect by binding to V1 receptors in the vascular smooth muscle and activating calcium channels. However, recent evidence suggests that effect of AVP is not uniform across all vascular beds. Low-dose AVP has been

![Fig. 5. Several alternate/adjunctive therapies have been developed based on identified cellular mediators involved in regulation of pulmonary vascular tone. Oxygen and iNO are the only established vasodilatory therapies for infants with PPHN and should be used as first-line therapies. Other therapeutic agents are currently under various stages of investigation. Cgmp, cyclic guanyl monophosphate; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase; PDE3, phosphodiesterase type 3; ET, endothelin; RCT, randomized control trial.](image-url)
shown to produce selective vasodilatation in coronary, cerebral, pulmonary, and renal vascular beds likely by stimulating release of endothelial nitric oxide while causing vasoconstriction in other vascular beds [45]. Systemic AVP therapy is widely used in treat-
ment of refractory vasodilatory shock in adults and pediatric pa-
tients and more recently has been successfully used for management of refractory hypotension in extremely low birth weight infants [46,47]. In addition, a retrospective study of neo-

tates with PPHN who were unresponsive to iNO therapy and who received treatment with AVP (received iNO for ≥ 4 h with no improvement in oxygenation) found a temporal association be-
tween AVP treatment and improvement in oxygenation with the effect starting within 3 h of initiating treatment [48]. Although AVP, by virtue of its biological properties, appears to be a promising agent for use in PPHN, it needs further systematic prospective evaluation. In our experience, a targeted approach to physiologic management is only effective in the setting of a patent ductus arteriosus with a right-to-left or bidirectional shunt, presumably secondary to its contribution to reduced PBF.

4.6. Management of RV dysfunction

Integral to the management of RV dysfunction is the determi-
nation of the relative contribution of altered RV loading conditions versus impaired myocardial performance. In some situations, the approach to treatment may include broad physiologic consider-
ation. There are few clinical indicators of the adequacy of RV per-
formance in neonates. Until recently direct visual assessment of RV performance by echocardiography was the most widely used method, but this is highly subjective and does not consider ventri-
cular loading conditions. Novel techniques using tricuspid anular plane systolic excursion index, tissue Doppler imaging, and the change in ventricular cavity fractional area can provide addi-
tional insights into the adequacy of RV systolic performance, and

normative data have recently been described for neonates during the transitional period [49]. Treatment strategies for acute RV dysfunction are derived from the pathogenic entities outlined pre-
iously. Major components include volume optimization, RV ino-
tropy enhancement, and RV afterload reduction (Fig. 4). As RV performance is highly volume dependent, it is important to correct hypovolemia as it may limit the pulmonary blood flow in a pressure-
passive circulation. However, excessive augmentation of RV preload may have a negative impact on cardiac output by increasing leftward deviation of the interventricular septum, limiting LV filling. Adequate oxygenation and lung recruitment are important to minimize hypoxic pulmonary vasoconstriction episodes, which further augment RV afterload and prohibit recovery of myocardial performance. Due to potential adverse hemodynamic effects, me-

chanical ventilation needs to be administered with caution and expertise. Higher tidal volume and positive end-expiratory pressure may increase pulmonary arterial pressure, worsen tricuspid regur-
gitation, and increase RV afterload [50]. In addition, positive end-

expiratory pressure may decrease RV pre-load by diminishing venous return. The decision to provide support directly augmenting RV systolic performance versus reducing RV afterload is challenging. In the setting of high oxygen requirements and echocardiography evidence of PPHN, initiation of iNO treatment to reduce RV afterload would appear prudent, although this has not been formally inves-
tigated. Low-dose intravenous prostaglandin E1 should be consid-
ered when the ductus arteriosus is closed or small and when there is evidence of impaired cardiac output. As discussed earlier, main-
taining a right-to-left shunt across the fetal channels will offload the RV and will augment systemic blood flow, albeit at the expense of blood oxygenation. The selection of an inotrope to augment ven-
tricular performance is dependent on systemic arterial pressure.

Dobutamine, the inotrope traditionally used in cardiac pump failure, works through primarily β1-adrenoreceptor-mediated increases in myocardial contractility and is the first-line agent in normotensive patients. Concomitant stimulation of β1-adrenoreceptor stimula-
tion in the systemic circulation induces vasodilation and decreases

afterload in a developmentally regulated manner [51]. In adults with acute PH, there is evidence that low-dose dobutamine (2 to 5 μg/kg/

min) increases CO and decreases PVR, whereas higher doses (5 to 10 μg/kg/min) only induce tachycardia and increase myocardial oxygen consumption without further improvements in PAP [52]. Higher doses of dobutamine might also impair diastolic function and thus decrease ventricular filling. Milrinone, a selective phosphodiesterase-3 (PDE3) inhibitor, also exerts inotropic and vaso-
dilatory properties and improves diastolic performance [1]. However, milrinone’s inotropic effect might be developmentally regulated because of the differential expression of phosphodies-
terase isoforms between fetal and postnatal life [53]. Although decreasing PVR and increasing RV systolic pressure may be desirable in the setting of a failing right ventricle and acute PPHN, milrinone’s use in the immediate postnatal period is thus limited by systemic vasodilation and hypotension. Like dobutamine, milrinone can be combined with iNO to augment pulmonary vasodilation while minimizing hypotension and tachyarrhythmias. There is some experimental evidence that, in the setting of 100% oxygen admin-
istration, iNO upregulates PDE3 expression [54]. Theoretically co-
administration of milrinone in this setting would appear to have biological plausibility through augmenting cAMP-related pulmo-
nary vasodilation. Epinephrine and/or norepinephrine increases inotropy through β1-adrenoreceptor agonism. Concomitant stimula-
tion of β1-adrenoreceptor increases RV perfusion pressure and cardiac output, but, according to findings in the developing swine, it might also increase in PVR and pulmonary artery pressure [55], Epinephrine. Finally, similar but not identical to the effects of epinephrine are the cardiovascular actions of dopamine, another vasopressor-inotrope often used in hypotensive neonates with PPHN in the clinical practice.

5. Role of targeted neonatal echocardiography in PPHN

Increasingly, neonatologists around the world are beginning to use bedside targeted neonatal echocardiography (TnECHO) or functional echocardiography to facilitate clinical decision-making for critically ill neonates in neonatal intensive care units [56,57]. A TnECHO is an ultrasound scan of the heart focused on acquiring clinically relevant real-time hemodynamic information related to cardiovascular health of the newborn. A major benefit of TnECHO is the ability to perform short longitudinal studies to help monitor disease progression and response to clinical interventions [58]. As the measurements are mostly obtained by physicians experienced in performing and interpreting TnECHO and directly involved in patient care, clinical integration of the acquired information is easier. Complete technical details of TnECHO training and meth-
odology are beyond the scope of this review and have been described elsewhere [58]. Given the non-specific nature of symp-
toms in neonates and low sensitivity and specificity of clinical signs, clinical integration of information obtained from a TnECHO study can help establish diagnosis, define the true nature and severity of the associated physiological derangements and provide measures to monitor response to treatments. As highlighted earlier, although PPHN is primarily a disorder of high PVR, it can be associated with a number of secondary hemodynamic alterations of varying severity. Whereas in some patients high PVR may be the only abnormality, in others it may be complicated by reduced PBF, right and/or left ventricular dysfunction and low systemic blood flow and perfusion pressure. Further, in some patients, failure of improvement with
vasodilator therapies may be because high PVR is truly unrespon-
sive to treatment, whereas in others it may be due to absence of
significant PPHN, as the cause of HRF was parenchymal lung dis-
ease. In addition, therapies not leading to immediate clinical
improvement in oxygenation are often deemed as a
‘failure’. In our experience, TnECHO can facilitate identification of a subclinical
response, where there are measureable improvements in cardio-
pulmonary indices even though the clinical picture does not change
immediately. It is plausible that in such patients the use of physi-
ologically appropriate adjunctive treatment may be a better
approach than discontinuation of the therapy perceived to be
ineffective. The TnECHO assessment in neonates with PPHN and a
structurally normal heart include: evaluation of pulmonary he-
modynamics; assessment of impact on systemic circulation; and
assessment of impact on right ventricular performance (Table 1). It
is important to be comprehensive, as any single echocardiographic
marker, when used in isolation, is unlikely to yield information
leading to clinical benefits. This problem is potentiated in neonates,
due to the small size of the anatomic structures interrogated,
therein increasing the possibility for erroneous results as well as a
higher degree of inter- and intra-observer variability. In addition,
there is a lack of validation studies and normative data for some of
the measurements in the neonate. Nevertheless, when the infor-
mation gathered from TnECHO is integrated with the clinical situ-
uation, it can provide significant physiological insights, allowing clinicians to take better-informed decisions. Accordingly, targeted
neonatal echocardiography should be used to complement rather
than replace clinical judgment.

6. Conclusion

In summary, PPHN is a widespread neonatal problem whose
hallmark clinical feature is oxygenation failure, yet it represents a
spectrum of physiologic contributors that must be considered when
making clinical decisions. Neonatal intensivists must recognize and
follow the standard therapeutic approach including the judicious use
of oxygen, the administration of INO and achievement of appropriate
lung recruitment. It is equally important not to lose sight of the
fundamental physiologic rationale, which forms the basis of this
approach and is based on management of elevated PVR. The latter is
most relevant when considering alternative pulmonary vasodilators
or drugs to support right ventricular performance. The use of TnECHO
may provide novel physiologic insights in patients who are critically
ill or refractory to standard approaches, enabling a more physiologi-
cally relevant approach to therapeutic interventions.

Table 1

<table>
<thead>
<tr>
<th>Use of targeted neonatal echocardiography in PPHN.</th>
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<tbody>
<tr>
<td><strong>Assessment of pulmonary artery resistance and pressure</strong></td>
<td><strong>Assessment of impact on left heart function and systemic circulation</strong></td>
<td><strong>Assessment of right heart function and pulmonary blood flow</strong></td>
</tr>
<tr>
<td>Quantitative: Calculation of RV systolic pressure using modified Bernoulli’s equation from measurement of peak velocity of TR or Doppler of PDA flow.</td>
<td>LV preload: Subjective assessment of Doppler of pulmonary venous flow and Doppler of flow across mitral valve in diastole.</td>
<td>RV contractility: Quantitative evaluation using recently described indices — measurement of tricuspid annular plane systolic excursion, tissue Doppler-derived peak systolic myocardial velocity at the base of the right ventricle and fractional area change; qualitative assessment of RV contractility and dilatation.</td>
</tr>
<tr>
<td>Qualitative: Estimation of RV systolic pressure in comparison to systemic systolic pressure — interventricular septal positioning at end systole; pattern of blood flow across PDA and PFO.</td>
<td>Systemic blood flow: Quantitative measurement of LV output and stroke distance in ascending aorta.</td>
<td></td>
</tr>
</tbody>
</table>

TR, tricuspid regurgitation; PDA, patent ductus arteriosus; PFO, patent foramen ovale; LV, left ventricle; RV, right ventricle.

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Practice points
- Persistent pulmonary hypertension represents a failure of the normal postnatal decline in pulmonary vascular resistance, which should form the basis for therapeutic interventions.
- Targeted neonatal echocardiography may provide novel physiologic insights, particularly when standard-of-care treatment options fail.
- Therapeutic strategies should focus on optimization of lung recruitment, pulmonary vasodilation, and supporting cardiac output.

Research directions
- Need to investigate the mechanistic role of right ventricu-ular performance in refractory patients.
- Evidence for alternative therapies is limited to pharma-
cological and case–control studies and, despite the
recognized logistical difficulties to perform well-designed
RCTs on neonates with PPHN, this should be another area
of future clinical research focus.

Conflict of interest statement
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References