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Therapy of pulmonary hypertension in neonates and infants

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Abstract

Pulmonary hypertension (PH) in newborns and infants can present in its idiopathic form or complicate a long list of other diseases. Most of these conditions are either pulmonary or cardiovascular in origin. In the present review our currrent knowledge regarding pathophysiology, structural changes, diagnosis, and available treatment options for PH in the age group below 1 year of age is summarized. New treatment options available in adults including endothelin receptor antagonists (ETRA) and phosphodiesterase (PDE) inhibitors are presented and the need for randomized controlled trials in newborns and infants is emphasized. Future candidates for pharmacotherapy of PH in infants include among others vasoactive intestinal polypeptide (VIP), PDE-3 and PDE-4 inhibitors, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and adrenomedullin (ADM).

Keywords: Persistent pulmonary hypertension of the newborn; Pulmonary arterial hypertension; Nitric oxide; Prostacyclin; Sildenafil; Bosentan

Abbreviations: 6MWD, 6-min walking distance; ADM, adrenomedullin; EPC, endothelial progenitor cells; ETRA, endothelin receptor antagonist; HMG-CoA, hydroxymethylglutaryl coenzyme A; MCT, monocrotaline; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal polypeptide.

Contents

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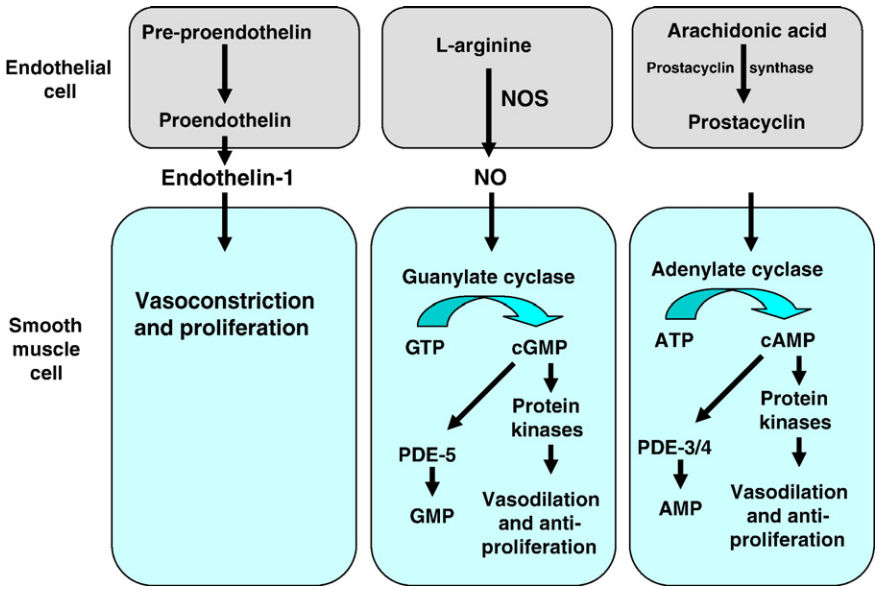
1. Introduction

Pulmonary hypertension (PH) covers a broad clinical spectrum ranging from transient neonatal condition to permanent disabling disease in infancy or childhood. A variety of perinatal conditions can trigger persistent PH of the newborn (PPHN; Dakshinamurti, 2005). In the majority of cases, PPHN can successfully be reversed by specific treatment of the underlying condition in addition to treatment of PH. Primary PPHN is a rare event, in which cases no triggering condition of PPHN can be identified. Treatment of PPHN consists of preferably selective pulmonary vasodilation, which was first made available by the introduction of inhaled nitric oxide (NO) into neonatal clinical practice in the early 1990s (Kinsella et al., 1992; Roberts et al., 1992). While starting with considerable enthusiasm for the new drug, neonatologists began to realize, that a certain proportion of newborns with clinical PPHN did not respond favorably to NO (Hoehn & Krause, 2001; Travadi & Patole, 2003). Clinical management of this subgroup of patients combined with economic considerations and transient decreased availability of NO combined to boost the development of alternative drugs, like phosphodiesterase-5 inhibitors (PDE) or endothelin-1 receptor antagonists (ETRA) to successfully treat PH. Advantages of the latter medications include a prolonged half-life and independence from inhalational equipment. Unfortunately, due to the low number of neonates and infants treated with these substances, there are currently neither randomized controlled trials nor much experience with long-term application of these drugs available.

2. Physiology of perinatal and postnatal changes

A prerequisite for efficient postnatal gas exchange in any newborn infant is the clearance of substantial amounts of fetal lung fluid (Jain & Dudell, 2006). Rapid clearance of fetal lung fluid is a key part of perinatal adaptation and is mediated in large part by transepithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells (Jain & Eaton, 2006). Failure to achieve this adaptation results in respiratory morbidity presenting as transient tachypnea of the newborn (term infant) or respiratory distress syndrome (preterm infant), depending on gestational age of the newborn. Particularly when uterine contractions are absent immediately prior to delivery, as in selective Cesarean section, there is no activation of the amiloride-sensitive sodium channels in the alveolar epithelial cells and therefore an increased risk of respiratory morbidity.

Regulation of pulmonary arterial resistance thus determining pulmonary blood flow is achieved by the interaction of 3 main players: NO, endothelin, and prostaglandins (Ziegler et al., 1995). Among these, endothelin increases pulmonary vascular resistance (PVR), whereas NO and prostaglandins lead to vasodilation and reduced vascular resistance (for details, see Fig. 1). Other genes and their products involved in the



pathogenesis of PH include prostacyclin synthase, serotonin transporters, serine elastases, matrix metalloproteinases (MMP), voltage-gated potassium (Kv) channels, angiotensin-converting enzyme (ACE), vascular endothelial growth factor (VEGF), carbamoyl phosphate synthase, and plasminogen activator inhibitor type 1 (PAI-1; Runo & Loyd, 2003). The ultimate effect on pulmonary vascular remodeling is a result of the interplay of these genetic factors, modifying genes, and environmental factors.

PVR is high in utero when pulmonary blood flow is limited to ~ 8% of total cardiac output and fetal oxygen requirements are met by placental blood flow (Lakshminrusimha & Steinhorn, 1999). Immediately after birth PVR decreases and continues to do so for the following 3 months (Haworth, 1995). The decrease in PVR leads to increases in pulmonary blood flow. Higher pressures in the left atrium and in the aorta lead to functional closure of the foramen ovale and reverse the intrauterine right-to-left shunting across the duct into a left-to-right shunting until the duct eventually closes. Any disruption in arterial oxygenation can reverse this process and lead to increased PVR and subsequent right-to-left shunt with clinical cyanosis.

3. Definition and incidence of pulmonary hypertension

The definition of PH is derived from adult patients and includes all individuals with mean pulmonary arterial pressures >25 mm Hg at rest or >30 mm Hg with exercise no matter what age (British Cardiac Society Guidelines and Medical Practice Committee, 2001). Since most of these measurements are performed by echocardiography, tricuspid regurgitation with a Doppler velocity of more than 2.5 m/sec has been used for the screening for PH. Most pediatric cardiologists would agree on a definition of PH where systolic pulmonary artery pressure exceeds 50% of systolic systemic pressure. These measurements are usually taken from either tricuspid regurgitation or from any known connection between systemic and pulmonary circulation (i.e., patent ductus arteriosus, ventricular septal defect; Tulloh, 2006).

The WHO classification of PH, which has been modified lastly in 2003 (Proceedings of the 3rd World Symposium on Pulmonary Arterial Hypertension, 2004) is shown in Table 1.

Conflicting data have been published concerning the incidence of PPHN. Whereas Farrow et al. (2005) quantified the incidence at 0.2% of live-born term infants, others gave a higher range of 0.43–6.8 per 1000 (Walsh-Sukys et al., 2000). The associated mortality rate of PPHN at the beginning of the 21st century was given at 10–20%, whereas earlier investigations reported mortality rates of up to 50% (Fox et al., 1977). According to a single center experience over almost 2 decades, a high proportion of infants who died from clinically suspected idiopathic PPHN were later found to have alveolar capillary dysplasia at autopsy (Tibballs & Chow, 2002). A decreasing incidence of PPHN could be expected from the falling incidence of meconium aspiration syndrome (Yoder et al., 2002), a disease which is frequently associated with

4. Structural changes in persistent pulmonary hypertension of the newborn/pulmonary hypertension

Most prominent histologic changes in PPHN include hypertrophy of the perivascular muscular layer in small and large pulmonary arteries (see Fig. 2**A**,**B**). Ultimately all 3 layers of the vascular wall are affected by thickening and extracellular matrix deposition, which is summarized by the term 'pulmonary vascular remodeling' (Jeffery & Wanstall, 2001). The latter condition consists of precocious development of muscle in intraacinar arteries, proliferation of adventitial connective tissue, and medial hypertrophy of preacinar arteries (Geggel et al., 1986).

5. Functional changes in persistent pulmonary hypertension of the newborn/pulmonary hypertension

Functional changes in PPHN/PH are mainly related to endothelial dysfunction and result in a dysbalance between

Table 1
Revised clinical classification of PH (adapted from Farber and Loscalzo, 2004; Simonneau et al., 2004)

Group I
Pulmonary arterial hypertension (PAH)
Idiopathic (IPAH)
Familial (FPAH)
Associated with (APAH)
●Collagen vascular disease
●Congenital systemic-to-pulmonary shunts
●Portal hypertension
●HIV infection
●Drugs and toxins
●Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
●Pulmonary veno-occlusive disease (PVOD)
●Pulmonary capillary hemangiomatosis (PCH)
PPHN
Group II
PH with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Group III
PH associated with lung diseases and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Group IV
PH due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
Group V
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary

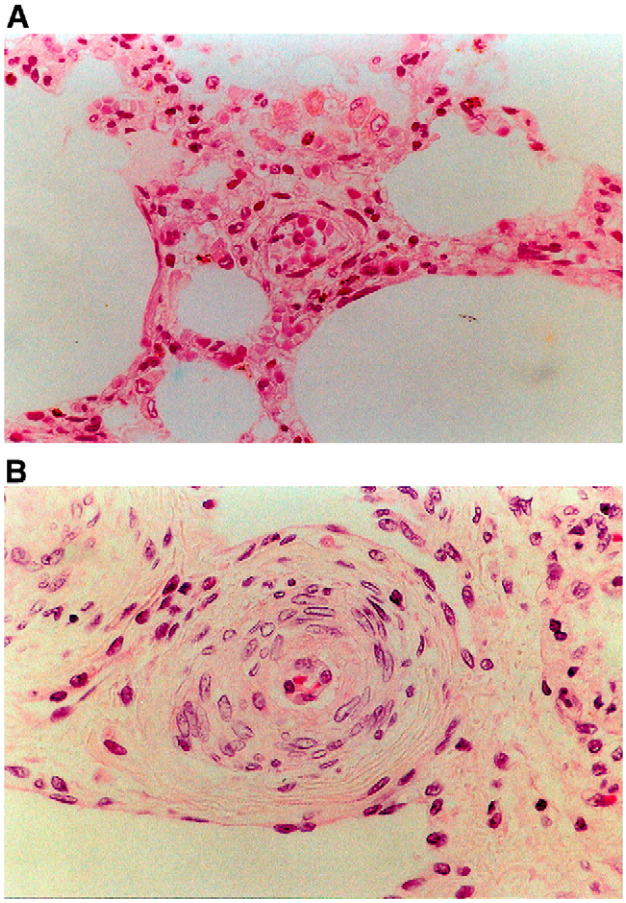


Fig. 2. (**A**) Hematoxylin–eosin staining of small pulmonary artery in control infant (magnification 400×, own data). (**B**) Hematoxylin–eosin staining of small pulmonary artery in an infant with PPHN (magnification 400×, own data).

vasodilation and vasoconstriction, in which vasoconstriction prevails. One factor contributing to vasoconstriction is high levels of endothelin-I, which have been shown in patients with PPHN (Vitali & Arnold, 2005). Another explanation for pulmonary arterial vasoconstriction in PPHN is the finding of diminished NO synthesis (Endo et al., 2001). Although endothelial NO synthase (eNOS) is upregulated in rapid PPHN (RPPHN), a particularly severe and fulminant form of PPHN (Hoehn et al., 2003), the net effect for the vessel diameter may still be vasoconstriction. Once hypoxia is present in PPHN it induces synthesis and release of VEGF (Liu et al., 1998). Increased levels of VEGF and smooth muscle proliferation can both be suppressed by NO. Others have shown beneficial effects of recombinant VEGF treatment in a lamb model of experimental PPHN (Grover et al., 2005). In this investigation VEGF improved endothelium-dependent vasodilation and reduced the severity of pulmonary vascular remodeling. Although VEGF expression is increased in newborns with PPHN (Lassus et al., 2001), the effects of VEGF may be altered by impaired signaling. An alteration of VEGF signaling has been suggested by animal studies of PH induced by either hypoxia or VEGF inhibition (Grover et al., 2003; by ductal ligation in the fetal lamb VEGF expression was markedly reduced (Grover et al., 2003). The postnatal model of hypoxia-induced PH found increased levels of VEGF but abolished vasodilation to VEGF potentially secondary to decreased expression of the VEGF receptor 2 (Nadeau et al., 2005).

6. Animal models

Several models of PH exist, the most frequently used among these are the injection of monocrotaline (MCT) and exposure to hypoxia (Campian et al., 2006). These animal models have not only been used to characterize the pathophysiology of PH and its sequelae such as right ventricular hypertrophy and failure but also to test novel therapeutic strategies. Others have used a specific rat strain, the Fawn-hooded rat, which tends to spontaneously develop PH under certain conditions (Le Cras et al., 1999; Tyler et al., 1999). The analysis of Campian et al. (2006) suggests that all approaches which have been successful in patients (most notably prostacyclin and ETRA) are also effective in various animal models. This is not true the other way around: results of animal experiments can often not been translated into efficacy in clinical studies, which presents a valid argument to perform the human studies in adults first, and thereafter in infants and children. Additional factors identified to affect pulmonary vascular resistance include carbon dioxide and pH. In a neonatal lamb model it was shown that elevated pH rather than decreased $PaCO_2$ during hyperventilation appears to be the major factor in moderating the response of the pulmonary vessels to acute hypoxia (Lyrene et al., 1985). Similar data have been obtained from infants after cardiopulmonary bypass for cardiac surgery. In this investigation increasing the arterial pH by the administration of sodium bicarbonate both lowered the pulmonary arterial pressure and increased the cardiac index, resulting in a decrease in pulmonary vascular resistance. These changes were observed without alteration in $PaCO_2$ (Chang et al., 1995). These observations should provide sufficient evidence to refrain from using hyperventilation in the clinical management of PH, whereas running the risk of decreasing cerebral blow flow below a critical threshold. Metabolic alkalosis apparently represents a highly efficient modulator of PH.

7. Neonatal disease

7.1. Primary persistent pulmonary hypertension of the newborn

The absence of any known trigger of PPHN in a term newborn presenting with cyanosis due to PH immediately postnatally suggests the presence of primary PPHN. In this condition PH appears to be caused by an abnormal pulmonary vascular bed rather than functional vasoconstriction due to other causes (Murphy et al., 1981). Intrauterine conditions like chronic hypoxia have been shown to result in muscularization of the pulmonary vasculature in animals and humans and to cause sustained hypertension after hypoxia is reversed (Rabi

7.2. Secondary persistent pulmonary hypertension of the newborn

A variety of perinatal and postnatal conditions can cause secondary PPHN: asphyxia, hypoxia, acidosis, hypoglycemia (Dakshinamurti, 2005), cold stress, infection, sepsis, meconium aspiration, lung hypoplasia, congenital diaphragmatic hernia (Perreault, 2006), respiratory distress syndrome, congenital pulmonary lymphangiectasia (Hoehn et al., 2006b), and congenital alveolar capillary dysplasia (Tibballs & Chow, 2002). Symptoms occur either immediately postnatally, such as in perinatal asphyxia or can be delayed by hours, like in evolving neonatal sepsis.

7.3. Clinical presentation of persistent pulmonary hypertension of the newborn

Neonates with PPHN present with severe cyanosis due to extrapulmonary shunting across the duct and the foramen ovale. Depending on the underlying condition, the associated tachydyspnea is more or less pronounced.

8. Pulmonary hypertension in infancy

Symptoms of infantile PH include breathlessness, fainting or chest pain during exercise, and exercise-induced syncope (Tulloh, 2006). A minority of infants presents with cyanosis, hemoptysis, or right heart failure with ankle edema or hepatomegaly (Rosenzweig & Barst, 2005).

9. Diagnosis of pulmonary hypertension

9.1. Newborns

PPHN can be most easily diagnosed by echocardiography even by the less experienced echocardiographer. Should this expertise be unavailable, simultaneous (or rapid sequential) transcutaneous measurements of pre- and postductal oxygen saturation can be used. A 5% or greater saturation decrease from pre- to postductal values is highly suggestive of the presence of extrapulmonary right-to-left shunting (Macdonald & Yu, 1992). High oxygen requirements without radiographic evidence of parenchymal pulmonary disease in any newborn infant should lead the clinician to suspect the presence of PPHN.

9.2. Infants

Echocardiography is the most frequently used investigation to screen for PH or to confirm or refute clinically suspected PH. Not only can cardiac causes of PH be identified (if present), the measurement of tricuspid regurgitation velocity enables the estimation of right ventricular pressures (Tulloh, 2006). Cardiac catheterization remains the gold standard for measurement of pulmonary artery pressures. This investigation specifically allows the quantification of the effects of PVR-lowering medications like NO (Atz et al., 1999) or prostacyclin (Mikhail

10. Therapy of pulmonary hypertension

10.1. Newborns

Therapy of PPHN in preterm and term infants is primarily directed at correction of the underlying condition (e.g., sepsis, hypoxia). Additionally oxygen saturation can be kept higher than in healthy term infants in order to decrease PVR by making use of the vasodilatory effect of oxygen. Due to the toxic effects of hyperoxia (retinopathy of prematurity; McColm et al., 2004) this is not an option in preterm infants. Prostacyclin (PGI_2) is a potent vasodilator of both pulmonary and systemic circulation acting via induction of cyclic adenosine monophosphate (Howard & Morrell, 2005). The nonselective effect of prostacyclins resulted in the development of the PGI_2 analogue iloprost, which can be applied by nebulization and therefore acts predominantly on the pulmonary circulation. The discovery of the identity of endothelium-derived relaxing factor (EDRF) as NO (Ignarro et al., 1987; Furchgott & Vanhoutte, 1989) led to the rapid clinical application of NO (Kinsella et al., 1992; Roberts et al., 1992). This molecule causes selective pulmonary vasodilation not only in adults but also in near-term and term infants; data on a large number of newborns have been summarized in a recent Cochrane analysis (Finer & Barrington, 2006). Altogether 14 randomized controlled trials have been included in this analysis comparing inhaled NO to either standard care without NO or allowing NO for rescue treatment. Inhaled NO significantly reduced the combined endpoint need for extracorporeal membrane oxygenation (ECMO) or death. Whereas mortality was hardly influenced, the main effect of inhaled NO was the avoidance of ECMO. No beneficial effect has been shown for subgroups of PPHN as for example infants with congenital diaphragmatic hernia (Finer & Barrington, 2006). Other medications studied in a small number of infants only include the PDE-5 inhibitor sildenafil (Baquero et al., 2006) and the nonselective ETRA bosentan (Galie et al., 2004). For both substances there is currently insufficient data in newborns in order to draw any conclusions for clinical practice.

10.2. Infants

Therapy of PH in children depends on the degree of PH in an individual patient and the extent of deterioration in specific situations (e.g., respiratory infection). One of the oldest drugs used for the treatment of PH is nifedipine, to which only a minority of infants respond favorably (Tulloh, 2006). Oxygen has been used traditionally for treatment not only under clinical conditions but also for home treatment. The vasodilatory response to high concentrations of oxygen belongs to the established tests during cardiac catheterization testing various vasodilatory conditions, including the inhalation of NO (Scheurer et al., 2006). The introduction of prostacyclin (PGI_2) into clinical practice brought a sustained benefit for hemodynamics and reduced mortality in comparison with historical data (McLaughlin et al., 2002). The major disadvantage for prolonged treatment consisted of PGI_2's short half-life of only 6 min and the necessity of an indwelling

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